



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 36

Alan R. Katritzky

Advances in

**Heterocyclic
Chemistry**

Volume 36

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Advances in

HETEROCYCLIC CHEMISTRY

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Preface

The current volume consists of four chapters. It commences with a comprehensive survey of the conformational rates and equilibria of saturated nitrogen-containing six-membered rings, authored by T. A. Crabb and the series editor. This is a subject wherein many of the past controversies have now been resolved and where it is now possible to provide a rather satisfying account.

R. J. Gallo, M. Makosza, H. J.-M. Dou, and P. Hassanaly present an authoritative review of applications of phase-transfer catalysis to heterocyclic chemistry that will be of great benefit to all involved with the synthesis of heterocycles.

Our understanding of the electrolysis of heterocycles has much increased lately, and it is appropriate that H. Lund and I. Tabaković have now updated the review written by the first-named author in Vol. 12 of *Advances in Heterocyclic Chemistry* (1970).

Finally, the chemistry of the pyrazolopyridines is surveyed for the first time by C. R. Hardy.

The contributions in this volume cover the literature through much of 1983.

ALAN R. KATRITZKY

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Advances in

Heterocyclic Chemistry

Volume 36

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Conformational Equilibria in Nitrogen-Containing Saturated Six-Membered Rings

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I. Introduction

A. SCOPE OF REVIEW

This review deals with conformational equilibria in piperidines, in piperidine derivatives in which ring methylenes are replaced by nitrogen, oxygen, and sulfur atoms, and in systems incorporating these rings in fused ring structures in which the additional rings are also six-membered. Fused-ring structures with other sizes of rings are generally not included, except for tropene.

Two previous reviews by one of the present authors have dealt (a) with the conformational preference for the *N*-H in six-membered rings (i.e., piperidines and hetero derivatives)¹ and (b) with the energy barrier to nitrogen inversion in six-membered rings.² The reader is referred to these for detailed treatment of these aspects. In the present treatment an attempt is made to list, with illustrations, the principal methods available for the investigation of heterocyclic conformational analysis. Then follows a treatment of individual ring systems in which the discussion centers on the conformational preferences of substituents on tertiary nitrogen and on ring carbon atoms, the energetics of nitrogen inversion, and phenomena arising from the presence of two or more heteroatoms in one ring.

Emphasis is placed on simply substituted free bases. The problems of conformational equilibria in *N*-alkylpiperidinium salts and *N*-quaternization reactions and the relationships of these to conformational equilibria in the free bases are not covered, since this area is a large one requiring separate treatment. In other relevant previous reviews, the topics include heterocyclic conformational analysis,³⁻⁷ interactions in azacyclic systems,⁸ the conformational analysis of piperidine,⁹ hexahydropyrimidines,^{10,11} hexahydropyridazines,¹² quinolizidines,¹³ the conformational analysis of bi- and polycyclic

¹ I. D. Blackburne, A. R. Katritzky, and Y. Takeuchi, *Acc. Chem. Res.* **8**, 300 (1975).

² A. R. Katritzky, R. C. Patel, and F. G. Riddell, *Angew. Chem., Int. Ed. Engl.* **20**, 521 (1980).

³ E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis." Wiley (Interscience), New York, 1965.

⁴ J. McKenna, *R. Inst. Chem. Lect. Ser.* No. 1, 1 (1966).

⁵ F. G. Riddell, *Q. Rev. Chem. Soc.* **21**, 362 (1967).

⁶ F. G. Riddell, "The Conformational Analysis of Heterocyclic Compounds." Academic Press, New York, 1980.

⁷ W. L. F. Armarego "Stereochemistry of Heterocyclic Compounds." Parts 1 and 2. Wiley (Interscience), New York, 1977.

⁸ A. R. Katritzky, *Bull. Soc. Chim. F.* 3585 (1967); *Quad. Ric. Sci.* **53**, 22 (1968).

⁹ J. B. Lambert and S. I. Featherman, *Chem. Rev.* **5**, 611 (1975).

¹⁰ E. L. Eliel, *Acc. Chem. Res.* **3**, 1 (1970).

¹¹ E. L. Eliel, *Angew. Chem., Int. Ed. Engl.* **11**, 739 (1972).

¹² S. F. Nelsen, *Acc. Chem. Res.* **11**, 14 (1978).

¹³ I. M. Skvortsov, *Usp. Khim.* **48**, 481 (1979).

systems by IR and ^1H -NMR spectroscopy,¹⁴ the applications of NMR spectroscopy to the study of the configurations and conformations of hetero rings,¹⁵ and the quaternization of N-alkyl cyclic bases.^{16,17}

B. GENERAL FEATURES OF CONFORMATIONAL EQUILIBRIA IN NITROGEN HETEROCYCLES

1. *Nature of Processes Involved*

At the heart of conformational processes in azacyclic systems lies the behavior of the conformationally mobile tertiary nitrogen atom. Nitrogen derivatives of the type $\text{NR}^1\text{R}^2\text{R}^3$, existing in more or less pyramidal form, undergo inversion of configuration via a planar transition state in which the nitrogen lone pair possesses pure *p* character. The process has been discussed in detail^{18–20}; bulky N substituents decrease ΔG^\ddagger for the process (pyramidal state destabilized by steric interactions), whereas electronegative α substituents increase ΔG^\ddagger . These effects are of great importance in 1,2-hetero systems (see Section III,C).

In the conformational analysis of six-membered rings, we deal with ring reversal equilibria and kinetics. To this is added in derivatives of piperidine the need to understand the equilibrium and kinetics of N inversion. Obviously, the sign of ΔG° is important for it determines the conformer favored at equilibrium. Less obviously, but of equal importance is the fact that the energy barrier between two conformations of N substituents consists of two "half barriers" $\Delta G_{\text{ax} \rightarrow \text{ts}}^\ddagger$ and $\Delta G_{\text{eq} \rightarrow \text{ts}}^\ddagger$ where ΔG° is the difference between the half barriers. It is important that in any precise discussion of the kinetics of N inversion that the half barrier under discussion should be clearly defined.² Neglect of this in the past has led to much confusion and controversy; the concept of half barriers is explained in detail in Ref. 2.

2. *Semiquantitative Considerations*

The concept of "size" of the nitrogen lone pair was introduced in early discussions²¹ of conformational equilibria, and detailed discussions and cal-

¹⁴ T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.* **71**, 109 (1971).

¹⁵ Yu. Yu. Samitov, *Khim. Geterotsikl. Soedin.*, 1443 (1980).

¹⁶ J. McKenna, *Top. Stereochem.* **5**, 275 (1970).

¹⁷ A. T. Bottini, in "Selective Organic Transformations" (B. S. Thyagarajan, ed.), p. 89. Wiley (Interscience), New York, 1970.

¹⁸ A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem., Int. Ed. Engl.* **9**, 400 (1970).

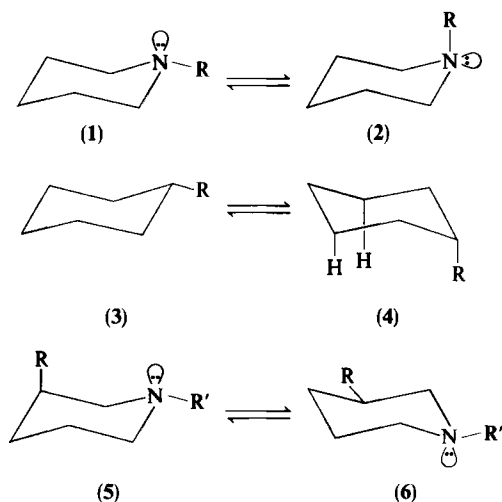
¹⁹ J. M. Lehn, *Fortschr. Chem. Forsch.* **15**, 311 (1970).

²⁰ J. B. Lambert, *Top. Stereochem.* **6**, 19 (1971).

²¹ D. H. R. Barton and R. C. Cookson, *Q. Rev., Chem. Soc.* **10**, 44 (1956).

culations on the size or steric requirements of electron pairs have been published.²²⁻²⁵ However, the lone pair can be regarded as having nondirectional behavior. The axial or equatorial preference ($1 \rightleftharpoons 2$) of a substituent on nitrogen is clearly of fundamental interest, but ascribing such a preference to the relative size of an axial lone pair or axial N substituent R is based on the classic concept of localized pairs.

Comparison of equilibria in carbocyclic and heterocyclic series (e.g., $1 \rightleftharpoons 2$, $3 \rightleftharpoons 4$, and $5 \rightleftharpoons 6$) illustrates the differences in conformational preferences in heterocyclic and carbocyclic systems. The C—N bond length (1.47 Å) is less than the C—C length (1.54 Å), so that the nonbonded interactions in **2** involving R and the syn axial C—H bonds should be significantly greater than in **4**. The axial orientation of R in **5** is also expected to be more favorable than in **4** because one of the syn axial interactions between R and a C—H bond in **4** is replaced by a syn axial interaction between R and the nitrogen atom and its associated lone pair of electrons.



Just as conformational behavior in cyclohexane has been explained semi-quantitatively in terms of "gauche-butane" interactions (cf. $3 \rightleftharpoons 4$, R = Me), corresponding "gauche-propylamine" (C—C—C—N) and other interactions can be used to discuss conformational equilibria involving heteroatoms.²⁶

²² N. L. Allinger and J. C. Tai, *J. Am. Chem. Soc.* **87**, 1227 (1965).

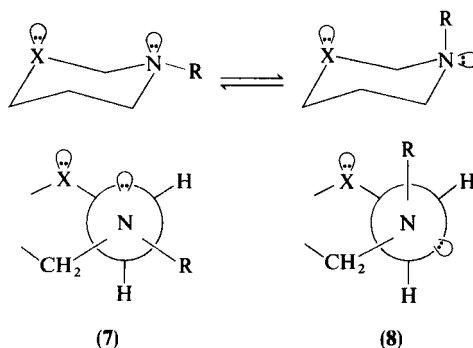
²³ N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Lett.*, 3729 (1967).

²⁴ A. R. Katritzky, in "Topics in Heterocyclic Chemistry" (R. N. Castle, ed.), p. 35. Wiley, New York, 1969.

²⁵ M. A. Robb, W. J. Haines, and I. G. Csizmadia, *J. Am. Chem. Soc.* **95**, 42 (1973).

²⁶ P. J. Brignell, K. Brown, and A. R. Katritzky, *J. Chem. Soc. B*, 1462 (1968).

In 1,3-heterocyclic systems the N substituent has an increased preference for the axial position as a result of the generalized anomeric effect.^{27,28,28a} This anomeric effect has been discussed^{29,30} in terms of a repulsion between parallel lone pairs of electrons, the "rabbit ears effect," which causes those conformations possessing parallel unshared electron pairs on nonadjacent atoms to be disfavored. This concept of the lone-pair–lone-pair repulsions influencing the equilibrium is not supported by calculations,²⁷ which give results corresponding to the original conception of the anomeric effect.³¹ The conformational preference is governed by a balance between attractive and repulsive interactions involving nuclei and electrons. Structures containing the maximum number of gauche interactions between lone electron pairs and polar bonds represent energy minima (the gauche effect). Thus, **8** is favored (gauche effect of adjacent polar bonds outweighs gauche effect of polar bond and two lone pairs) in the equilibrium $7 \rightleftharpoons 8$. An alternative conception of the anomeric effect has been described³² in terms of a donation of lone-pair electrons on nitrogen into the antibonding C—X orbital, which is possible only in **8**.



Lone-pair–lone-pair interactions are in part responsible for the conformational features of the hexahydropyridazine and related systems,¹² and these are discussed in Section III,C,2.

²⁷ S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc. B*, 136 (1971).

²⁸ R. U. Lemieux, *Pure Appl. Chem.* **25**, 527 (1971).

^{28a} G. A. Jeffrey, J. A. Pople, and L. Radom, *Carboh. Res.* **25**, 117 (1972).

²⁹ E. L. Eliel, *Kem. Tidskr.* **81**, 22 (1969).

³⁰ E. L. Eliel, R. O. Hutchins, and L. D. Kopp, *J. Am. Chem. Soc.* **90**, 7174 (1968).

³¹ R. U. Lemieux and P. Chü, *Abst., 133rd Natl. Meet., Am. Chem. Soc.* p. 31N (1958).

³² C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.* **4**, 39 (1970).

II. Methods of Investigating Conformations and Conformational Equilibria

A. COMPUTATIONAL METHODS

Computer programs have been developed³³ to determine the geometry of six-membered heterocycles by strain energy minimization procedures. Bond lengths were treated as invariant, and equilibrium bond angles were taken from corresponding three-membered units. Bond-angle distortion energies required a knowledge of force constants, which were not available for nitrogen systems from the literature, but estimates were used in the calculations, which did show that the calculated geometries were insensitive, over a small range, to small variations in the actual force constants used. A symmetrical threefold sinusoidal barrier was used in the estimation of torsional distortion. Finally, nonbonded interactions, assumed to be covered in part by the bond-angle distortion and torsional distortion terms, were omitted from the calculation. Minimization procedures gave the angles between ring planes shown in Fig. 1 and the bond and torsional angles shown in Fig. 2. Molecular mechanics methods are also available.^{33a}

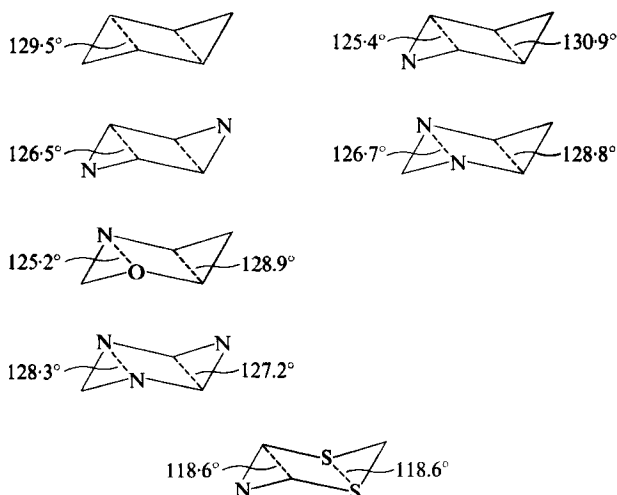


FIG. 1. Angles between ring planes in heterocycles.³³ Planes are defined by dotted and adjacent solid lines.

³³ I. D. Blackburne, R. P. Duke, R. A. Y. Jones, A. R. Katritzky, and K. A. F. Record, *J. C. S. Perkin II* 322 (1973).

^{33a} U. Burkert and W. L. Allinger, "Molecular Mechanics," ACS Monograph No. 177, (1972).

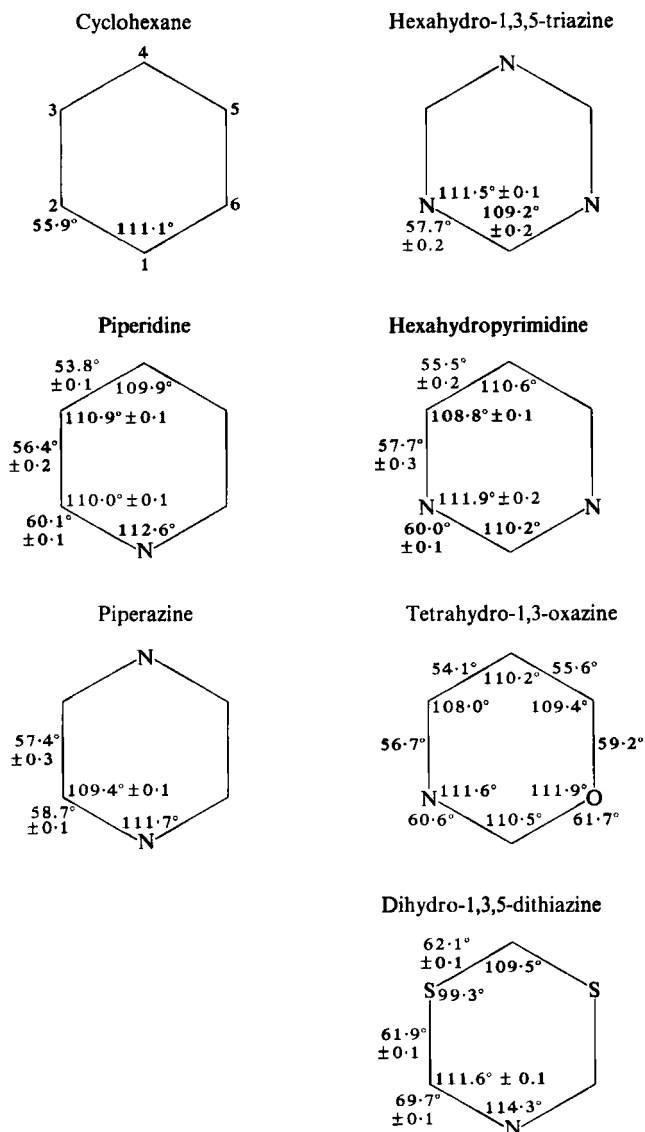
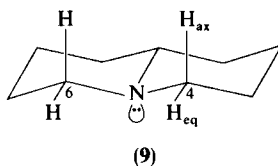


FIG. 2. Endocyclic bond and torsional angles in heterocycles.³³ (Within rings: endocyclic bond angles. Outside rings: torsional angles subtended by ring bonds.)

B. NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

1. ^1H -NMR Chemical Shifts of Protons
Adjacent to Nitrogen

a. *Background to Δ_{ae} Criterion of Conformation.* A remarkable feature of the NMR spectrum of quinolizidine (**9**) is the very large difference in chemical shift between the C-4 axial and equatorial protons ($\Delta_{ae} = 0.93$ ppm).³⁴ However, in trifluoroacetic acid solution the axial protons (of the quinolizidine conjugate acid) absorb at about δ 3.0 and the equatorial protons at δ 3.5, a difference of only 0.5 ppm, comparable to the difference in chemical shifts between the axial and equatorial protons in cyclohexane (0.48 ppm). This reduction in chemical shift difference on protonation was taken as an indication that the nitrogen lone pair was involved in the shielding mechanism. It was suggested³⁴ that a partial participation of the lone pair of electrons in a $\sigma^* \text{C}-\text{H}_{ax}$ orbital on the adjacent carbon atom occurs, leading to an increase in electron density at the proton anti-coplanar to the nitrogen lone pair. Thus 4(ax)-H will be preferentially shielded relative to 4(eq)-H and a large Δ_{ae} will be observed. Cis-fused quinolizidine derivatives are characterized by small Δ_{ae} values because the lone pair bisects the $\alpha\text{-CH}_2$ group.^{35,36}



The Δ_{ae} criterion was applied to the problem of the piperidine equilibrium (**10** \rightleftharpoons **11**) by examining the ^1H -NMR spectrum of the deuterio derivatives **12**, **13**, and **14** at -85°C when ring inversion is slow on the NMR time scale.³⁷ The Δ_{ae} values are recorded in Table I. The preferred conformation for the N-substituted piperidines **13** and **14** was assigned as lone-pair axial because for these compounds Δ_{ae} values were similar to those in quinolizidine. However, in piperidine (**12**), where the Δ_{ae} value is similar to that in cyclohexane, the lone pair was assumed to occupy the equatorial position in the preferred conformation. In support of this contention, protonation of

³⁴ H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964).

³⁵ F. Bohlmann, D. Schumann, and H. Schulz, *Tetrahedron Lett.*, 173 (1965).

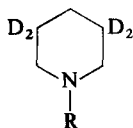
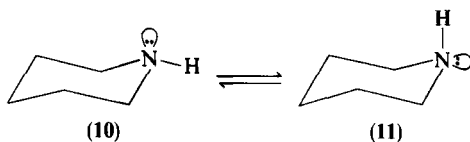
³⁶ F. Bohlmann, D. Schumann, and C. Arndt, *Tetrahedron Lett.*, 2705 (1965).

³⁷ J. B. Lambert and R. G. Keske, *J. Am. Chem. Soc.* **88**, 620 (1966); J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *ibid.* **89**, 3761 (1967).

TABLE I
 Δ_{ac} VALUES AND J_{gem} VALUES FOR PIPERIDINES (12–14)³⁷

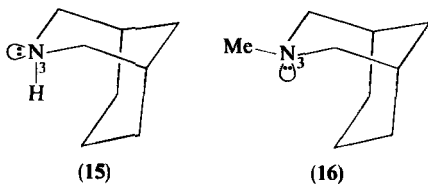
Compound	Solvent	Δ_{ac} (ppm)	$-J_{ac}$ (Hz)
12	CH ₃ OD	0.43	11.9
	Toluene- <i>d</i> ₈	0.54	11.2
13	CH ₃ OD	0.93	11.4
	Toluene- <i>d</i> ₈	1.10	11.0
14	CH ₃ OD	0.99	10.7
	Toluene- <i>d</i> ₈	1.06	10.2

the nitrogen atom altered Δ_{ac} for the *N*-Me and the *N*-*t*-Bu compounds, but not for piperidine.



- (12) R = H
 (13) R = Me
 (14) R = *t*-Bu

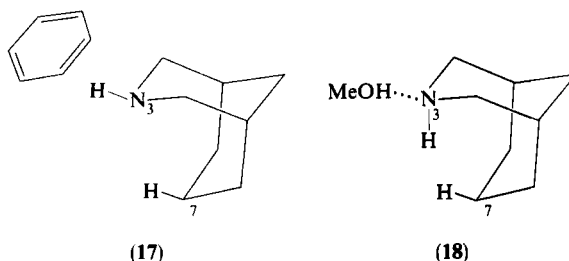
The Δ_{ac} values (at 60 MHz) observed for 3-azabicyclo[3.3.1]nonane and its *N*-methyl derivative were 0.08 and 0.67 ppm respectively, a decrease of 0.5–0.6 ppm compared to the Δ_{ac} values for the corresponding piperidines. On this evidence the conformations **15** and **16** were assigned to these compounds.³⁷



However, there are two assumptions implicit in this treatment: (a) that a small isotropic substituent (e.g., methyl) would have the same effect on both

axial and equatorial protons of a methylene group, thus not affecting Δ_{ac} appreciably, and (b) that an axial lone pair of electrons causes selective shielding of vicinal axial protons. These were questioned.³⁸ In particular, an equatorial methyl group preferentially shields a vicinal axial proton in a range of cyclic compounds,³⁹ and a large part of the observed Δ_{ac} in *N*-methylpiperidine could be due to the differential shielding by the *N*-methyl group.

On the basis of a comparison of the solvent dependence of chemical shift values of the *N*-H proton in 3-azabicyclo[3.3.1]nonane [δ (CDCl₃) 1.41, δ (C₆H₆) 0.77] and in piperidine [δ (CDCl₃) 1.41, δ (C₆H₆) 1.01], it was suggested³⁸ that conformation **17** is preferred for 3-azabicyclo[3.3.1]nonane, because hydrogen bonding involving the *N*-H atom in conformation **15** should be hindered by the endo 7-hydrogen atom.



The addition of methanol to benzene solutions of 3-azabicyclo[3.3.1]nonane results in large shifts to high field of the endo 7-hydrogen, normally found at low field because of the proximity of the nitrogen lone pair of electrons. These shifts are best explained by a change in conformation from **17** to **18** so that the nitrogen lone pair of electrons can become hydrogen bonded to the methanol. Because this change is not accompanied by any detectable difference in the chemical shift values of the C-2 and C-4 methylene group protons, the orientation of the lone pair of electrons has no appreciable effect on the chemical shift values of the adjacent methylene group.³⁸

Booth and Little⁴⁰ observed a chemical shift difference (Δ_{ac}) of about 0.4 ppm for the C-2 and C-6 methylene protons in 4-methylpiperidine, which was assumed to exist as an equilibrium containing ~95% of the C-methyl equatorial conformation. *N*-Methylation of 4-methylpiperidine caused an upfield shift of 0.22 ppm for the C-2 equatorial proton and of 0.68 ppm for the C-2 axial proton. Comparison of these values with those observed for the proton adjacent to methyl groups in cyclohexane led these authors to the

³⁸ M. J. T. Robinson, *Tetrahedron Lett.*, 1153 (1968).

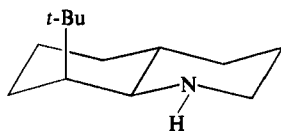
³⁹ A. Segré and J. I. Musher, *J. Am. Chem. Soc.* **89**, 706 (1967).

⁴⁰ H. Booth and J. H. Little, *Tetrahedron* **23**, 291 (1967).

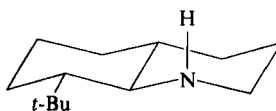
conclusion that quantitative assessment of the stereospecific shielding effect of the nitrogen lone pair was difficult and that the *N*-alkyl group could be of importance in the shielding process.

Lambert and Keske⁴¹ quantitatively assessed the relative contributions made by an adjacent lone pair of electrons on nitrogen and by an adjacent methyl group to the observed chemical-shift differences between the equatorial and axial protons in piperidine derivatives by comparisons (Table II) between the shifts in cyclohexane and piperidine series, assuming that the chair distortions in both molecules are approximately the same. The lone-pair effect on Δ_{ae} was considered to have a possible range from 0.35 to 0.65 ppm and the maximum alkyl effect to be 0.3 ppm. The small $\delta\Delta_{\text{ae}}$ (Δ_{ae} piperidine – Δ_{ae} piperidine hydrochloride) of 0.06 ppm for piperidine was taken as evidence for the predominance of the *N*-H_{ax} conformer, and the $\Delta\delta_{\text{ae}}$ of 0.50 ppm for *N*-methylpiperidine evidence for the predominance of the *N*-Me_{eq} conformer. However, the comparison of Δ_{ae} values in methanol with those in CCl₄ and CDCl₃ raises the problem of solvation and lessens the value of these results.

The Δ_{ae} in piperidine of 0.48 ppm is increased to 0.66 ppm (for the 6-methylene protons) in 3,3-dimethylpiperidine (measurements in CH₂Cl₂ solution below coalescence temperature for ring inversion). This was taken as an indication of an increase in *N*-H_{eq} conformer in the latter compound.⁴² Measurements on decahydroquinolines however, showed⁴³ the insensitivity of this parameter to *N*-H orientation (e.g. **19** and **20** gave Δ_{ae} values of 0.61 and 0.54 ppm, respectively).



(19)



(20)

Plots of Δ_{ae} against the percentage of lone-pair axial conformer (estimated by dipole-moment measurements) for some monocyclic heterocyclic compounds with differing *N*-alkyl substitution showed no correlation.⁴⁴ This is to be expected because the nature of the *N*-alkyl substituent also affects Δ_{ae} ⁴⁰ (Table III).

⁴¹ J. B. Lambert and R. G. Keske, *Tetrahedron Lett.*, 2023 (1969).

⁴² J. B. Lambert, D. S. Bailey, and B. F. Michel, *Tetrahedron Lett.*, 691 (1970); *J. Am. Chem. Soc.* **94**, 3812 (1972).

⁴³ E. L. Eliel, V. S. Rao, F. W. Vierhapper, and G. Z. Juaristi, *Tetrahedron Lett.*, 4339 (1975); F. W. Vierhapper and E. L. Eliel, *J. Org. Chem.* **44**, 1081 (1979).

⁴⁴ P. J. Halls, R. A. Y. Jones, A. R. Katritzky, M. Snarey, and D. L. Trepanier, *J. Chem. Soc. B*, 1320 (1971).

TABLE II
A COMPARISON OF Δ_{ac} VALUES FOR SOME CYCLOHEXANE AND PIPERIDINE
DERIVATIVES (NMR SPECTRA AT 60 MHz)⁴¹

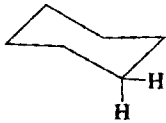
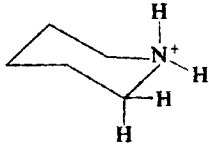
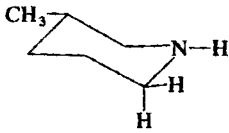
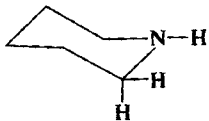
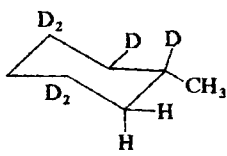
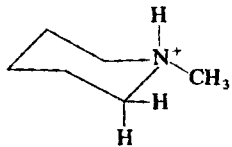
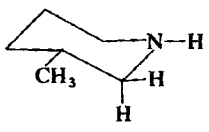
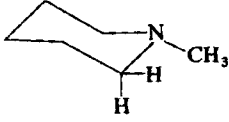
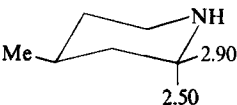
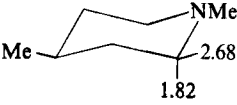
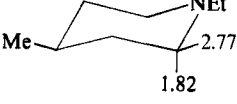
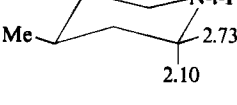
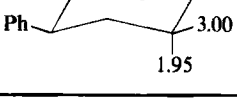
Solvent	Compound	Δ_{ac} (ppm)
CS ₂		0.48
CD ₃ OD		0.37
CDCl ₃		0.48
CD ₃ OD		0.43
CCl ₄		0.75
CD ₃ OD		0.45
CDCl ₃		0.78
CD ₃ OD		0.95

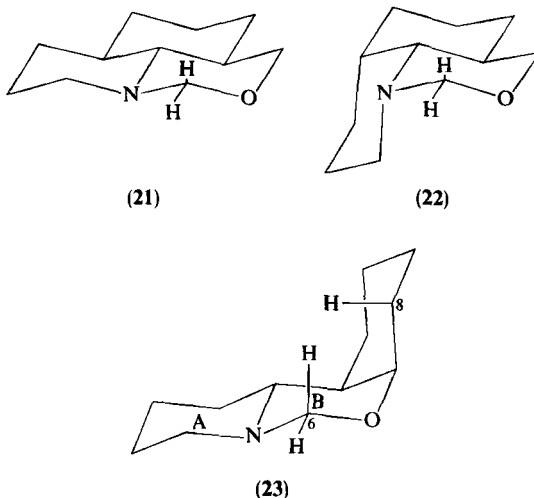
TABLE III
CHEMICAL SHIFTS OF α -METHYLENE PROTONS
(CCl₄) IN *N*-ALKYLPYPERIDINES⁴⁰

Structure	Δ_{ae} (ppm)
	0.40
	0.86
	0.95
	0.63
	1.05

b. *Conclusions and Use of the Δ_{ae} Criterion.* We conclude that differential effects of the N substituent in the *N*-axial and *N*-equatorial conformations is probably the major influence on Δ_{ae} of adjacent CH₂ groups and that the differential influence of axial-equatorial lone pairs is uncertain and likely to be small. In decahydroquinolines unsubstituted at nitrogen, Δ_{ae} is insensitive to lone-pair orientation.⁴³

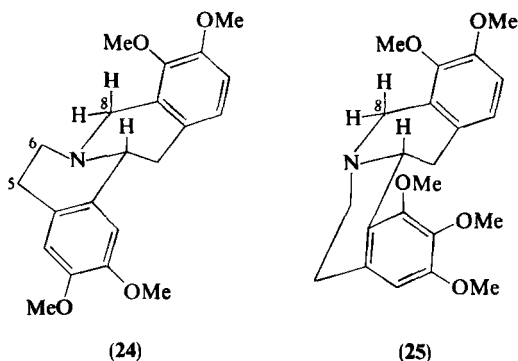
However, Δ_{ae} can still be used in suitable cases as an indication of conformation, particularly for polycyclic compounds. Thus Δ_{ae} measurements on *N*-CH₂X protons may be used to establish the *cis* or *trans* nature of the ring fusion in 1,3-heterocyclic systems. For example, the *trans*-fused perhydropyrido[3,2,1-*i,j*][3,1]benzoxazine (**21**) shows Δ_{ae} 0.84 ppm, indicative of the anti-coplanar CH-nitrogen lone-pair geometry, whereas the *cis*-fused isomer (**22**), in which the nitrogen lone pair bisects the CH₂ group, shows Δ_{ae} 0.12 ppm.⁴⁵

⁴⁵ T. A. Crabb and C. H. Turner, *J. C. S. Perkin II*, 1778 (1980).



Long-range effects on the chemical shifts of $N\text{-CH}_2$ protons must be taken into account when using the Δ_{ae} criterion. Thus, Δ_{ae} ($N\text{-CH}_2\text{O}$) in **23**⁴⁶ is 0 ppm, although the AB ring fusion is trans, as a result of deshielding⁴⁷ of the 6(ax)-proton by the C-8 methylene group.

Although the magnitudes of Δ_{ae} for the C-8 methylene protons in dibenzo- $[a,g]$ quinolizidines differ from those in quinolizidines, use may be made of Δ_{ae} in conformational assignments.⁴⁸ For example, in tetrahydropalmatine (trans-fused) (**24**) Δ_{ae} is 0.70 ppm, whereas in *O*-methylcapaurine (cis-fused) (**25**) Δ_{ae} is 0.38 ppm.

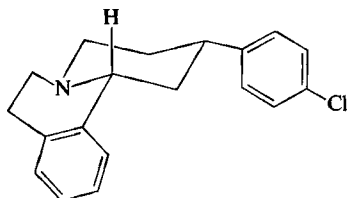


⁴⁶ T. A. Crabb and E. R. Jones, *Tetrahedron* **26**, 1217 (1970).

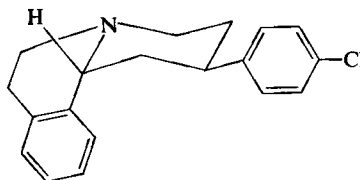
⁴⁷ H. Booth, *Tetrahedron* **22**, 615 (1966).

⁴⁸ D. Tourwé, G. Van Binst, and T. Kametani, *Org. Magn. Reson.* **9**, 341 (1977).

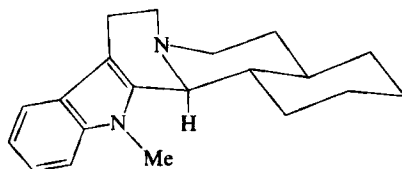
c. *Chemical Shifts of Angular Protons in Quinolizidines.* ^1H -NMR determinations of the positions of conformational equilibria in benzo[*a*]quinolizidines and indolo[2,3-*a*]quinolizidines have relied on the chemical shift of the angular proton.⁴⁹ For example, the *trans*-fused compound **26** shows absorption for the angular proton (anti-coplanar with nitrogen lone pair) at δ 3.8, whereas the *cis*-fused isomer **27**, in which the angular proton is gauche to the lone pair, shows absorption at δ 4.0. In these compounds, absorption to high or low field of δ 3.8 may indicate the nature of the ring fusion: however, long-range shielding effects may affect this, and in the *trans-anti-N*-methyl inside yohimbane (**28**), for example, the angular proton absorbs at δ 3.65, although the quinolizidine moiety is *cis*-fused.⁵⁰ Conformational assignments based on this parameter are discussed in Section III,B,3.



(26)



(27)



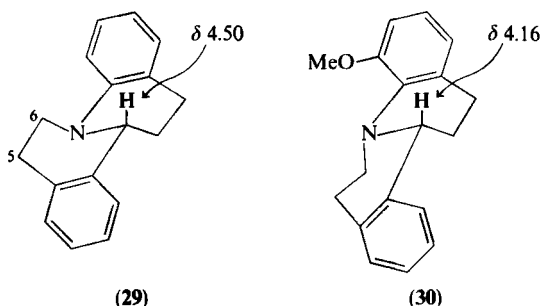
(28)

The chemical shift of the angular proton in benzo[*c*]quinolizidines will differ from that in quinolizidine itself as a result of delocalization of the lone pair electrons over the aromatic ring in certain conformations. Examples are provided by **29** and **30**. In *trans*-fused **29**, the nitrogen lone pair is delocalized over the aromatic ring and thus the anti-coplanar shielding mechanism is lost and the angular proton absorbs to low field of that in the *cis* conformation **30**.⁵¹

⁴⁹ M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Am. Chem. Soc.* **86**, 3364 (1964)

⁵⁰ G. C. Morrison, W. A. Cetenko, and J. Shavel, Jr., *J. Org. Chem.* **32**, 2768 (1967).

⁵¹ D. Tourwé, W. Van den Brandt, and G. Van Binst, *Bull. Soc. Chim. Belg.* **87**, 427 (1978).



2. Proton-Proton Geminal Coupling Constants in Methylene Groups Adjacent to Nitrogen

a. *Factors Affecting J_{gem} .* The value of the proton-proton geminal coupling constant (J_{gem}) is sensitive to changes in the molecular environment of the particular methylene group.⁵²⁻⁵⁴ The major factors affecting the magnitude of J_{gem} in $N-CH_2$ groups are discussed below, with particular emphasis on the influence of adjacent lone-pair orbitals on J_{gem} .

i. *The internal $N-CH_2-X$ angle.* A plot of J_{gem} (Hz) against the $C-CH_2-C$ internal bond angle θ in carbocyclic systems is shown in Fig. 3.⁵³ As the angle becomes smaller, i.e., as the amount of s character in the $C-H$ bond increases, the coupling constant becomes less negative. Presumably similar relationships hold for $N-CH_2-X$ units.

ii. *The inductive effect of α substituents.* The presence of an electronegative substituent adjacent to a methylene group causes the inductive removal of electrons from the symmetric methylene orbital and leads to less negative values of J_{gem} ^{55,56} (see Table IV).

iii. *The effect of an adjacent heteroatom.* Molecular orbital theory⁵⁴ predicts that back donation of α -heteroatom lone pairs of electrons into the antisymmetric methylene molecular orbital will result in a positive contribution to J_{gem} . The efficiency of this electron shift is dependent upon the degree of overlap, and hence the dihedral angle between the lone pair and the adjacent CH_2 bonds. The contribution to J_{gem} is predicted to be at a minimum when the lone pair bisects the $H-H$ internuclear axis of the CH_2

⁵² R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron* **25**, 4681 (1969).

⁵³ R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron, Suppl.* **7**, 355 (1966).

⁵⁴ J. A. Pople and A. A. Bothner-By, *J. Chem. Phys.* **42**, 1339 (1965).

⁵⁵ M. Karplus, D. H. Anderson, T. C. Farrar, and H. S. Gutowsky, *J. Chem. Phys.* **27**, 597 (1957).

⁵⁶ H. J. Bernstein and N. Sheppard, *J. Chem. Phys.* **37**, 3012 (1962).

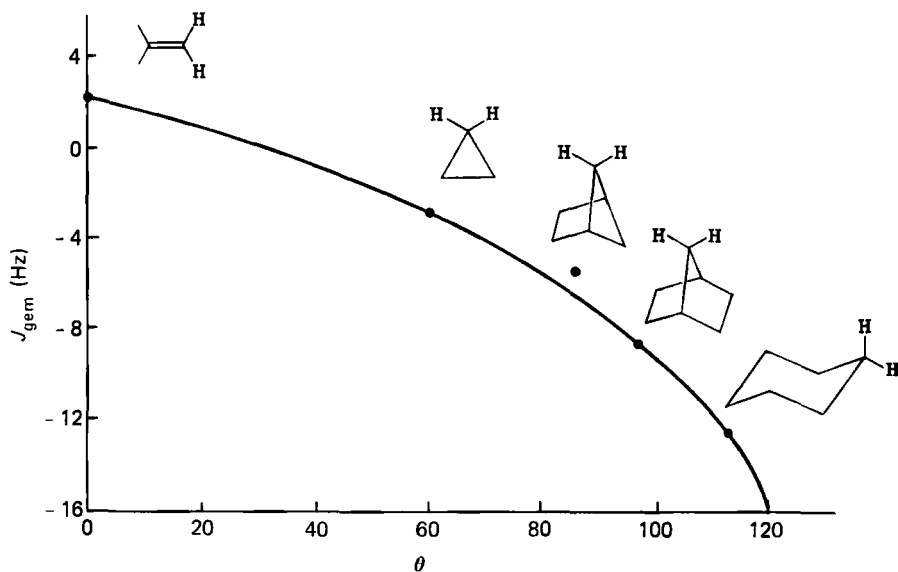


FIG. 3. The variation of J_{gem} with the C—C—C internal angle θ .⁵³

group. The maximum positive contribution occurs when the lone pair and an adjacent C—H bond are in an eclipsed relationship. This predicted dependence of the back donation upon the dihedral angle between the heteroatom lone-pair orbitals and the adjacent C—H bond has been demonstrated.^{57,58}

TABLE IV
THE EFFECT OF ELECTRONEGATIVE
SUBSTITUENTS ON J_{gem}

Compound	J_{gem} (Hz)
CH ₄	-12.4 ⁵⁵
CH ₃ OH	-10.8 ⁵⁶
CH ₃ Cl	-10.8 ⁵⁶
CH ₃ Br	-10.2 ⁵⁶
CH ₃ I	-9.2 ⁵⁶

⁵⁷ R. C. Cookson and T. A. Crabb, *Tetrahedron* **24**, 2385 (1968).

⁵⁸ M. Anteunis, *Bull. Soc. Chim. Belg.* **75**, 413 (1966).

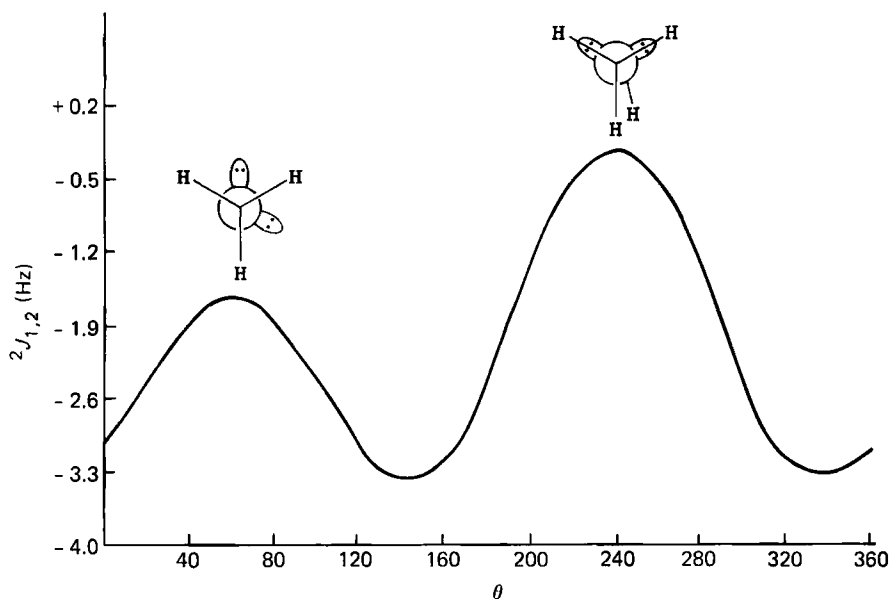


FIG. 4. Plot of $^2J_{1,2}$ against the dihedral H^1COH angle θ for methanol. (Reprinted with permission from Ref. 59. Copyright 1970 American Chemical Society.)

b. *Possible Difficulties in Use of J_{gem} as a Conformational Criterion.* A theoretical treatment of methanol,⁵⁹ summarized in Fig. 4, shows the variation of $^2J_{1,2}$ with the dihedral H^1COH angle θ between H^1 and the hydroxyl hydrogen. A similar relationship exists between J_{gem} in N-CH_2 groupings⁶⁰ and the dihedral angle θ between the nitrogen lone pair of electrons and the CH_2 bonds (Fig. 5), and this should in principle allow assignment of conformation.

Although substantial agreement exists between estimates of position of conformational equilibria for derivatives of the 1,3-heterobicyclic systems based on dipole-moment measurements and J_{gem} values⁶¹ (Section III,D), a linear relationship between J_{gem} and the percentage of lone-pair axial conformer in a series of compounds is only to be expected if ring strain and substituent effect variations are minimized. In reduced 1,3-heterocyclic systems, the changes in N substituent from methyl to *tert*-butyl with the related changes in hybridization at nitrogen must play an important part in deter-

⁵⁹ G. E. Maciel, J. W. McIver, Jr., N. S. Ostlund, and J. A. Pople, *J. Am. Chem. Soc.* **92**, 4151 (1970).

⁶⁰ P. J. Chivers and T. A. Crabb, *Tetrahedron* **26**, 3389 (1970).

⁶¹ I. D. Blackburne, A. R. Katritzky, D. H. Read, P. J. Chivers, and T. A. Crabb, *J. C. S. Perkin II*, 418 (1976).

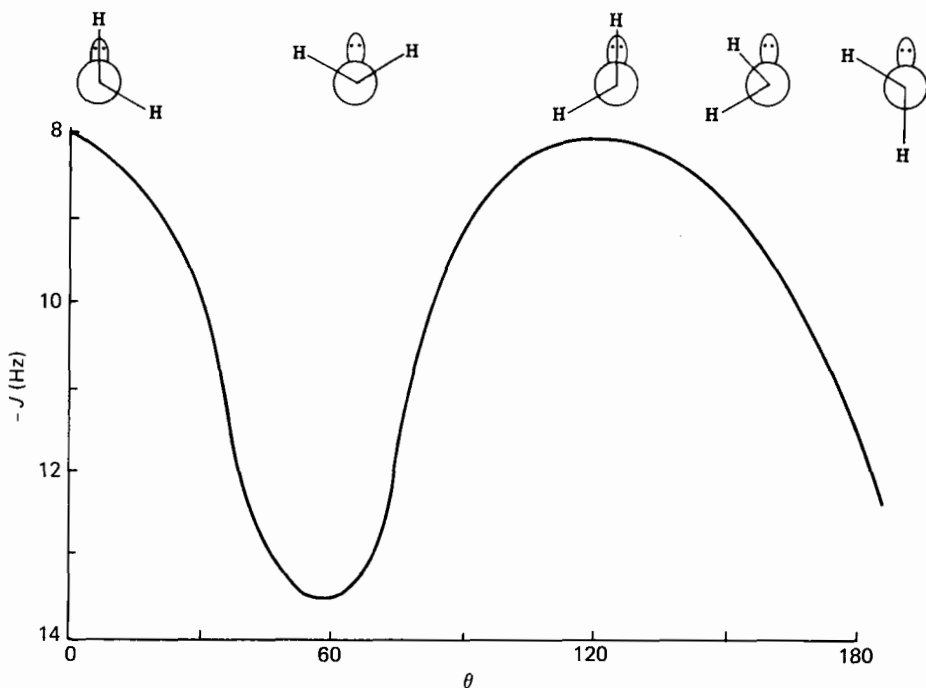
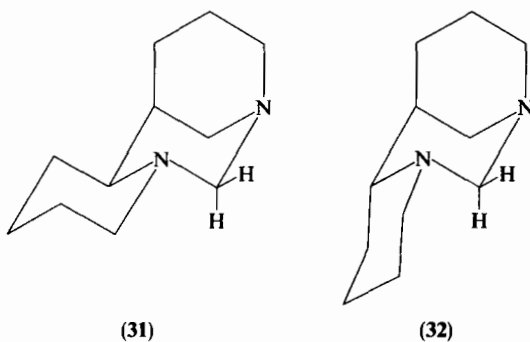


FIG. 5. The variation of J_{gem} in a N-CH_2 moiety with the dihedral angle θ between the C-H bond and the nitrogen lone pair.⁶⁰

mining the magnitude of J_{gem} . Even the locked compounds **31** ($J_{\text{gem}} = 11.3$ Hz) and **32** ($J_{\text{gem}} = 10.5$ Hz), with formally similar $\text{N-CH}_2\text{-N}$ geometry, possess differing J_{gem} values.⁶⁰ Thus the J_{gem}/θ relationship is expected to be valid only in a series of closely related compounds.

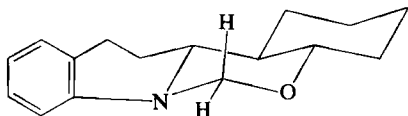


Some of the objections raised⁴⁴ against J_{gem}/θ relationships may no longer be valid, as some of the earlier estimates of lone-pair axial conformer

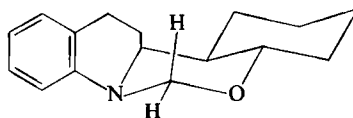
based on $^1\text{H-NMR}$ and dipole moments are now known to be in error. This matter is treated in detail in Section III,D,1,b (see Fig. 12) and in Section III,D,3,d [see discussion of the conformation equilibria in *trans*-decahydroquinazolines (**329–334**)].^{62,63}

c. *Application of J_{gem} as a Conformation Criterion.* Bearing in mind all the factors affecting J_{gem} , this parameter is of considerable use in assigning predominant conformations, especially in saturated 1,3-heterocyclic systems. A selection of values for locked derivatives is given in Table V.

Deviations from the values listed in Table V occur when the nitrogen atom is attached to an aromatic ring, permitting overlap of the nitrogen lone pair and the aromatic ring orbitals. For example, in the 8,9,10,11,11a,11b,12,13-octahydro-7a*H*-quino[1,2-*c*][1,3]benzoxazines (**33**) and (**34**), the anti-isomer **33**, in which delocalization of the nitrogen lone pair is possible, shows a more negative J_{gem} (–11.1 Hz) for the *N*-CH₂O protons than in *trans*-fused perhydropyrido[1,2-*c*][1,3]oxazines (–7.5 Hz). However, the *syn* isomer (**34**), in which the nitrogen lone-pair orbital and the aromatic orbitals are orthogonal, shows only a slightly reduced coupling constant (–8.7 Hz).⁶⁴

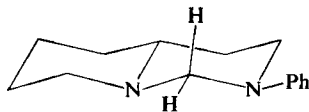
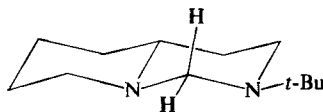


(33)



(34)

This effect is also shown by comparison of the coupling constants in the perhydropyrido[1,2-*c*]pyrimidines **35** and **36**,⁶⁵ *trans*-fused dibenzo[*a,f*]quinolizidine (**29**) ($J_{6\text{ax},6\text{eq}}$ – 12.7 Hz),⁵¹ and quinolizidine (J_{gem} – 11.3 Hz).⁶⁶ The similar coupling constants of the C-1 and C-3 methylenes in the


 $J_{\text{gem}} = -10.5 \text{ Hz}$
(35)

 $J_{\text{gem}} = -8.8 \text{ Hz}$
(36)

⁶² W. L. F. Armarego, R. A. Y. Jones, A. R. Katritzky, D. M. Read, and R. Scattergood, *Aust. J. Chem.* **28**, 2323 (1975).

⁶³ W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc. C*, 2502 (1971).

⁶⁴ T. A. Crabb and J. S. Mitchell, *J. C. S. Perkin II*, 1592 (1977).

⁶⁵ T. A. Crabb and R. F. Newton, *Tetrahedron* **26**, 701 (1970).

⁶⁶ R. Cahill, T. A. Crabb, and R. F. Newton, *Org. Magn. Reson.* **3**, 263 (1971).

TABLE V
 J_{gem} VALUES IN 1,3-HETEROCYCLIC SYSTEMS

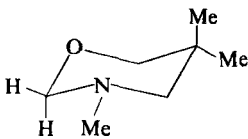
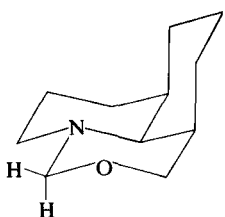
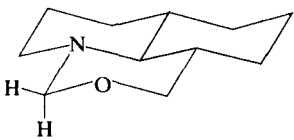
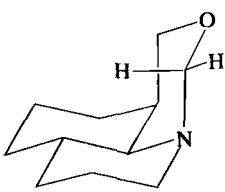
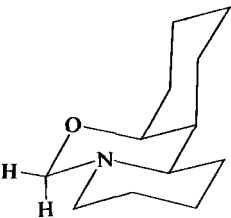
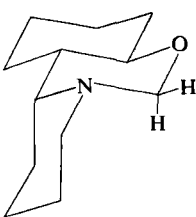
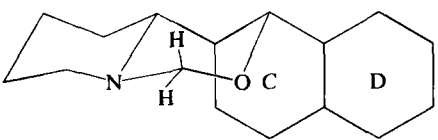
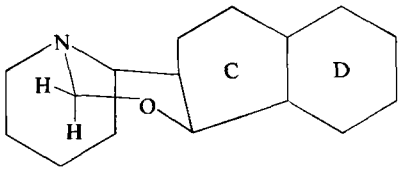
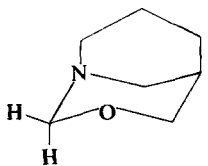
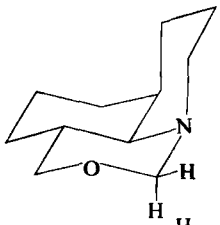
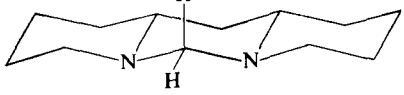
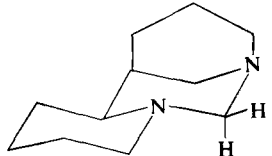
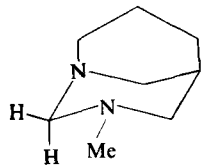
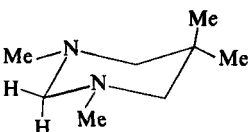
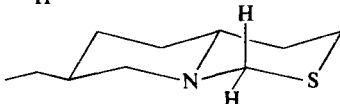
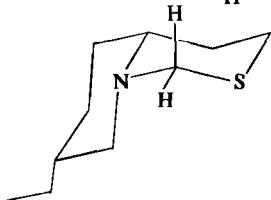
Compound	Solvent/conditions	$-J_{\text{gem}}$	Reference
	CF ₂ Cl ₂ -79°C	7.5	272
	CDCl ₃	7.7	45
	CDCl ₃	7.5	45
	CDCl ₃	7.5	45
	CCl ₄	7.2	46
	CCl ₄	7.4	46

TABLE V (continued)

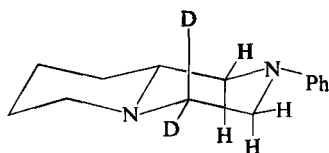
Compound	Solvent/conditions	$-J_{\text{gem}}$	Reference
 (3 different C/D isomers)	CDCl_3	7.5, 7.6, 7.6	280
 (2 different C/D isomers)	CDCl_3	7.1, 7.2	280
	CDCl_3	10.5	272
	CDCl_3	10.8	45
	CDCl_3	8.5	137
	CDCl_3	11.3	60
	CDCl_3	11.2	291

(continued)

TABLE V (continued)

Compound	Solvent/conditions	$-J_{\text{gem}}$	Reference
	CH_2Cl_2 -60°C	7.9	291
	CDCl_3	11.9	101
	CDCl_3	12.8	101

perhydropyrido[1,2-*a*]pyrazine **37**⁶⁷ to that in trans-fused quinolizidine, however, suggests little delocalization of the nitrogen lone pair.



$$J_{1\text{ax},1\text{eq}} = -11.1 \text{ Hz}$$

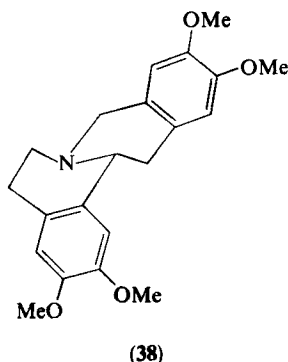
$$J_{3\text{ax},3\text{eq}} = -11.7 \text{ Hz}$$

(37)

The variation in the half-chair-type conformations for dibenzoquinolizidines may affect J_{gem} in certain positions. Thus a comparison of J_{gem} for the C-8 methylene protons in *O*-methylcapaurine (**25**) (-16.4 Hz), xylopinine (**38**) (-14.4 Hz), and tetrahydropalmatine (**24**) (-15.9 Hz) shows⁴⁸ the more negative J_{gem} expected for the cis-fused than for the trans-fused isomer but an unexpected difference in J_{gem} between the two trans-fused isomers. This may be a result of the vicinity of an OMe group or of small changes in the conformation of the ring caused by the different aryl substitution pattern resulting in different contributions from the aromatic ring π orbitals to J_{gem} .⁶⁸

⁶⁷ R. Cahill and T. A. Crabb, *J. C. S. Perkin II*, 1374 (1972).

⁶⁸ M. Barfield and D. M. Grant, *J. Am. Chem. Soc.* **85**, 1899 (1963).



3. Proton-Proton Vicinal Coupling Constants and the R-Value Method

Vicinal coupling constants in HC—CH fragments are related to the dihedral angle ϕ by the relationship

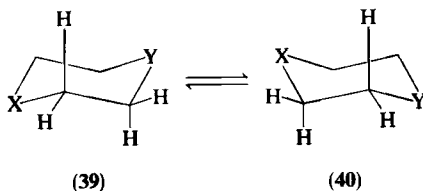
$$J_{HH} = A \cos^2 \phi$$

Substitution of an electronegative substituent X into the fragment as in HC—CHX reduces J_{HH} and for substituted ethanes

$$J_{HH} = J_{(\text{in ethane})}(1 - 0.07 \Delta X)$$

where ΔX is the difference in electronegativity between H and X. In addition, J_{HH} is sensitive to the HCC bond angle and the C—C bond length.⁶⁹

In a six-membered ring heterocyclic system existing as two equivalent conformers **39** and **40**, two couplings may be measured from the NMR spectrum and, assuming that $J_{ac} = J_{ea}$,

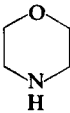
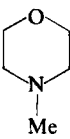
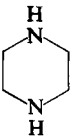
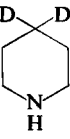
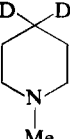


$$J_{\text{trans}} = 1/2(J_{aa} + J_{ee})$$

$$J_{\text{cis}} = 1/2(J_{ae} + J_{ea}) = J_{ac}$$

⁶⁹ E. Hiroike, *J. Phys. Soc. Jpn.* **15**, 270 (1960); M. Karplus, *J. Am. Chem. Soc.* **85**, 2870 (1963); H. S. Gutowsky, M. Karplus, and D. M. Grant, *J. Chem. Phys.* **31**, 1278 (1959); J. Ranft, *Ann. Phys. (Leipzig)* [7] **8**, 322 (1961).

TABLE VI
R VALUES OF SOME
AZACYCLIC SYSTEMS^{70,71}

Compound	R^a	Torsional angle deduced
	2.19	58°
	2.18	58°
	2.15	58° ^b
	2.09	57°
	2.06	57°

^a $R = J_{\text{trans}}/J_{\text{cis}}$ (see text).

^b 56° from X-ray structure.

In such systems, electronegativity effects of X and Y will be minimized in the ratio

$$R = J_{\text{trans}}/J_{\text{cis}}$$

For an ideal chair with $\phi = 60^\circ$, $R = 2$ (Table VI). Deviations from $R = 2$ are taken as indications of departure from ideal chair conformation. For $R > 2.5$, an appreciably puckered-chair conformation is indicated and for $R < 1.8$, a flattened-chair.^{70,71}

⁷⁰ J. B. Lambert, *J. Am. Chem. Soc.* **89**, 1836 (1967).

⁷¹ J. B. Lambert, *Acc. Chem. Res.* **4**, 87 (1971).

An expression has been developed^{32,72} relating R to the $X-C-C-Y$ dihedral angle ψ , assuming trigonal projection symmetry in the XCH_2CH_2Y fragment. Substituting $\phi_{aa} = 120 + \psi$, $\phi_{ee} = 120 - \psi$, and $\phi_{ac} = \psi$ in the Karplus expressions $J_{HH} = A \cos^2 \phi$, and using these to calculate J_{trans} and J_{cis} , gives $\cos^2 \psi = 3/(2 + 4R)$.

4. ¹³C-NMR Spectroscopy

a. Chemical Shifts. ¹³C-NMR^{72a} shifts have been reported for a large number of piperidines,^{73–77a} quinolizidines,^{78,79} and decahydroquinolines,^{80–85} and reviews of ¹³C-NMR spectra of quinolizidine derivatives⁸⁶ and of alkaloids containing the quinolizidine moiety⁸⁷ are available. Of most use in these stereochemical assignments is the γ -effect;⁸⁸ this is the shielding of a carbon nucleus gauche to another carbon relative to the ¹³C-NMR shift of such a carbon in the corresponding anti relationship. This is illustrated by the C-6 shifts in the trans- and cis-fused protoberberines **41** and **42**,⁸⁹ by the C-6 shifts in yohimbine (**43**) and pseudoyohimbine (**44**),⁹⁰ and by the deoxynupharidines **45** and **46**.⁹¹ The two types of cis-fused quinolizidines exemplified by **42** (aryl ring-A outside cis conformer) and **44** (aryl ring inside

⁷² H. R. Buys, *Recl. Trav. Chim. Pays-Bas* **88**, 1003 (1969).

^{72a} E. L. Eliel and K. M. Pietrusiewicz, in "Topics in ¹³C-NMR Spectroscopy" (G. C. Levy, ed.) **3**, 171 (1979).

⁷³ G. Ellis and R. G. Jones, *J. C. S. Perkin II*, 437 (1972).

⁷⁴ H. Booth and D. V. Griffiths, *J. C. S. Perkin II*, 842 (1973).

⁷⁵ D. Wendisch, H. Feltkamp, and U. Scheidegger, *Org. Magn. Reson.* **5**, 129 (1973).

⁷⁶ I. Morishima, K. Yoshikawa, K. Okada, T. Yonezawa, and K. Goto, *J. Am. Chem. Soc.* **95**, 165 (1973).

⁷⁷ J. B. Lambert, D. A. Netzel, H. Sun, and K. K. Lilianstrom, *J. Am. Chem. Soc.* **98**, 3778 (1976).

^{77a} E. L. Eliel, D. Kandasamy, C.-Y. Yen, and K. D. Hargrave, *J. Am. Chem. Soc.* **102**, 3698 (1980).

⁷⁸ R. T. Lalonde and T. N. Donvito, *Can. J. Chem.* **52**, 3778 (1974).

⁷⁹ F. Bohlmann and R. Zeisberg, *Chem. Ber.* **108**, 1043 (1975).

⁸⁰ H. Booth and D. V. Griffiths, *J. C. S. Perkin II*, 111 (1975).

⁸¹ H. Booth, D. V. Griffiths, and M. L. Jozefowicz, *J. C. S. Perkin II*, 751 (1976).

⁸² H. Booth and J. M. Bailey, *J. C. S. Perkin II*, 510 (1979).

⁸³ E. L. Eliel and F. W. Vierhapper, *J. Org. Chem.* **41**, 199 (1976).

⁸⁴ F. W. Vierhapper and E. L. Eliel, *J. Org. Chem.* **42**, 51 (1977).

⁸⁵ F. W. Vierhapper, E. L. Eliel, and G. Zúñiga, *J. Org. Chem.* **45**, 4844 (1980).

⁸⁶ D. Tourwé and G. Van Binst, *Heterocycles* **9**, 507 (1978).

⁸⁷ T. A. Crabb, *Annu. Rep. NMR Spectrosc.* **8**, 1 (1978).

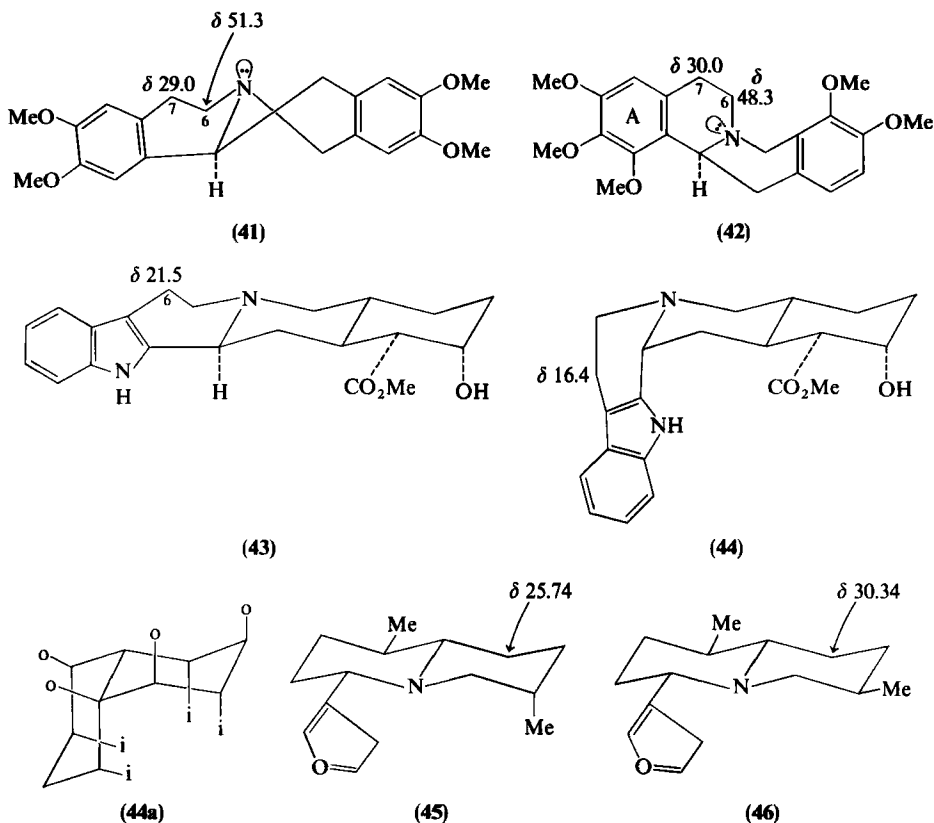
⁸⁸ D. K. Dalling and D. M. Grant, *J. Am. Chem. Soc.* **89**, 6612 (1967).

⁸⁹ T. Kametani, A. Ujiie, M. Ihara, K. Fukumoto, and H. Koizumi, *Heterocycles* **3**, 371 (1975).

⁹⁰ E. Wenkert, H. P. S. Chawla, C.-J. Chang, D. W. Cochran, E. W. Hagaman, J. C. King, and K. Orito, *J. Am. Chem. Soc.* **98**, 3645 (1976).

⁹¹ R. T. Lalonde, T. N. Donvito, and A. I.-M. Tsai, *Can. J. Chem.* **53**, 1714 (1975).

cis conformer)^{91a} may be differentiated by reference to the chemical shifts of the benzylic methylene carbon nuclei (30.0 for C-7 in **42** and 16.4 for C-6 in **44**). Similar γ -effects to those arising from a C—H bond are exhibited by the nitrogen lone pair⁹⁰ and γ -effects in CCNC units are greater than in CCCC units, presumably as a result of the shorter C—N bond length.⁸⁶

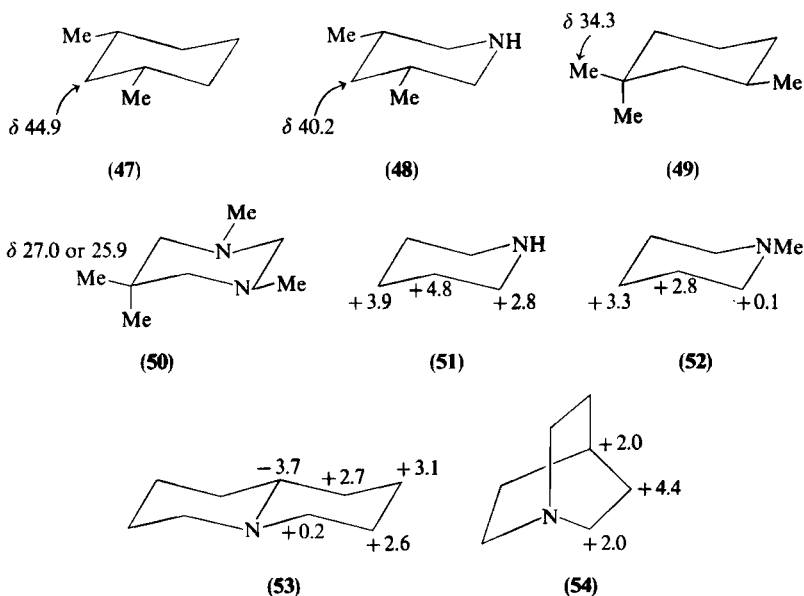


Marked upfield shifts of C* in the anti-periplanar NCCC* moiety have been noted.⁹² This is illustrated by comparison of the chemical shifts (CDCl₃) in **47** and **48** and in **49** and **50**.⁹² Upfield shifts of axial methyl carbon nuclei α to nitrogen in *trans*-decahydroquinolines are observed for

^{91a} The "inside" and "outside" positions of axial substituents in a cis-fused decaline ring are shown in structure **44a**.

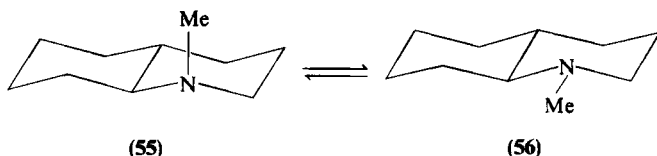
⁹² E. L. Eliel, W. F. Bailey, L. D. Kopp, R. L. Willer, D. M. Grant, R. Bertrand, K. A. Christensen, D. K. Dalling, M. W. Duch, E. Wenkert, F. M. Schell, and D. W. Cochran, *J. Am. Chem. Soc.* **97**, 322 (1975).

N-Me_{eq} conformers (relative to *N*-Me_{ax} conformers). No corresponding shifts are seen in the spectra of the corresponding *N*-H compounds.⁸⁵



Stereochemically dependent upfield protonation shifts (trifluoroacetic acid) in piperidine derivatives have been claimed.⁷⁶ The similarities between shifts of the β carbon in piperidine (51) and quinuclidine (54) and in 52 and 53 were taken to indicate similar lone-pair orientations, but in the light of work described in Section III,A this interpretation must be dropped.

The use of ^{13}C -NMR chemical shifts in estimating the position of conformational equilibria may be illustrated by reference to the conformational equilibria of the *N*-methyl group in *N*-methyl-*trans*-decahydroquinoline (55 \rightleftharpoons 56).^{93,94}



If δ_{ax} and δ_{eq} are the chemical shifts of the *N*-Me group carbon nuclei in 55 and 56 respectively, and δ is the observed chemical shift of the *N*-Me

⁹³ F. W. Vierhapper and E. L. Eliel, *J. Am. Chem. Soc.* **96**, 2257 (1974).

⁹⁴ E. L. Eliel and F. W. Vierhapper, *J. Am. Chem. Soc.* **97**, 2424 (1975).

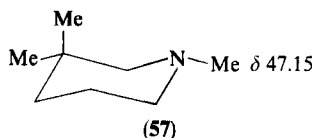
carbon for the equilibrium, then

$$\delta = n_{\text{eq}}\delta_{\text{eq}} + n_{\text{ax}}\delta_{\text{ax}}$$

where n_{eq} and n_{ax} are the mole fractions of **56** and **55**, respectively. Because $n_{\text{eq}} + n_{\text{ax}} = 1$ and δ may be observed, the mole fractions may be estimated if δ_{eq} and δ_{ax} are known

For the equilibrium $\mathbf{55} \rightleftharpoons \mathbf{56}$, δ_{ax} may be selected from entries 6, 7, and 8 in Table VII and δ_{eq} from entries 4 and 5 in Table VII. Comparison with the observed δ (entries 1, 2, and 3 in Table VII) provides an estimated $-\Delta G^\circ$ of 2.28 kcal mol⁻¹. As the value of δ is close to δ_{eq} , this should be regarded as a lower limit ΔG° .

The reliability of this method depends among other things on the suitability of the model compounds used for the estimation of δ_{eq} and δ_{ax} . Thus for the *N*-methylpiperidine equilibrium, it was assumed that **57** provided

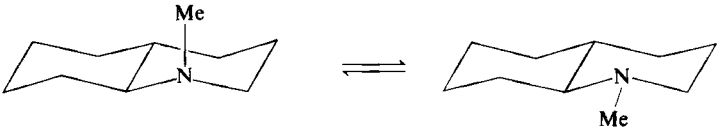
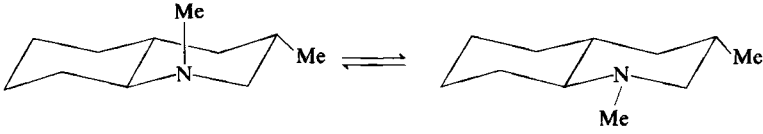
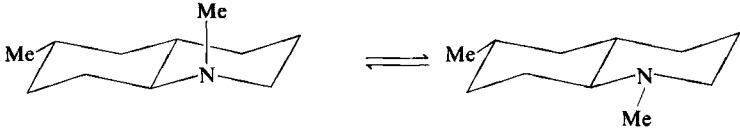
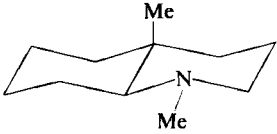
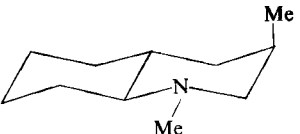
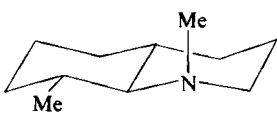
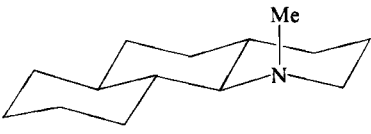
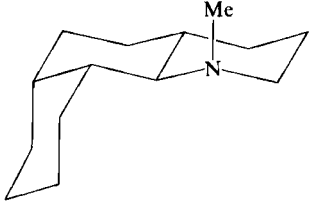


an acceptable value for δ_{eq} . Because no suitable models exist for the *N*-Me_{ax} conformer, δ_{ax} was calculated from values contained in Table VII. On this basis ΔG° for the *N*-methylpiperidine equilibrium ($\mathbf{N-Me_{ax}} \rightleftharpoons \mathbf{N-Me_{eq}}$) was estimated^{93,94} as -1.69 kcal mol⁻¹. However, this value was later withdrawn:⁸⁴ it differs markedly from the accepted value of -2.7 kcal mol⁻¹ (see Section III,A,1,b). Apart from the uncertainties of the model compounds, errors in ΔG° arise in this method as a result of the small differences between δ_{eq} and δ . Estimation of free-energy differences between the chair and twist-chair forms of 3,3-dimethylpiperidines by measurement of temperature gradients of ¹³C-NMR chemical shifts has been shown⁹⁵ to be unreliable.

In the application of Anet's equations (see Section II,B,5 below) to the estimation of ΔG^\ddagger and ΔG° by low temperature ¹³C-NMR spectroscopy, the magnitude of $\Delta\nu$ (the chemical shift difference between the exchanging sites) is required. Because this cannot always be observed, resort has to be made to some indirect method of estimation of $\Delta\nu$. This has been done, for example, in the case of the 1,2,4-trimethylhexahydro-1,2,4-triazine equilibrium (Section III,F,3) by estimating the chemical shifts in the various conformers from chemical shift effects based on model systems (Table VIII). Utilization of

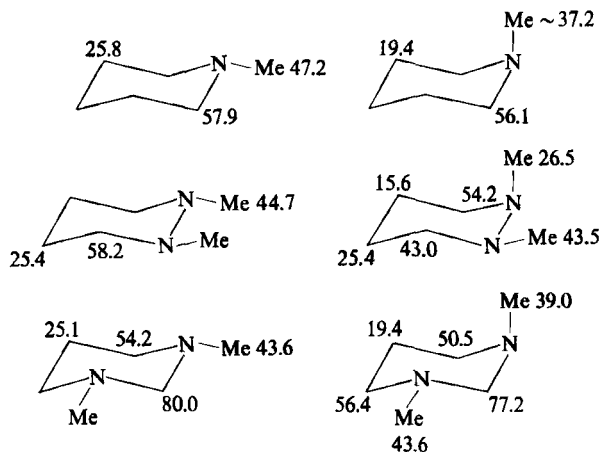
⁹⁵ J. B. Lambert, A. R. Vagenas, and S. Somani, *J. Am. Chem. Soc.* **103**, 6398 (1981).

TABLE VII
¹³C-NMR N—Me CHEMICAL SHIFTS IN *N*-METHYL-*trans*-DECAHYDROQUINOLINE^{93,94}

Entry	Structure	δ_{NMe}
1		42.52 ^a
2		42.32 ^a
3		42.77 ^a
4		43.04
5		42.94
6		33.18
7		33.10
8		32.97

^a Average.

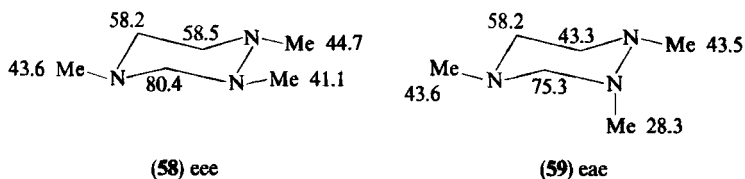
TABLE VIII
¹³C-NMR SHIFTS FOR *N*-METHYLPYRIDINE,⁹⁴
 1,2-DIMETHYLHEXAHYDROPYRIDAZINE,²⁵⁰
 1,3-DIMETHYLHEXAHYDROPYRIMIDINES,²⁸⁹ AND CHEMICAL SHIFT EFFECTS
 ARISING FROM STRUCTURAL MODIFICATION OF *N*-METHYLPYRIDINE⁹⁶



Chemical Shift Effect

Substituent	<i>N</i> -Me _{eq} piperidine			<i>N</i> -Me _{ax} piperidine		
	NMe	C-2	C-3	NMe	C-2	C-3
α NMe _{eq}	-2.5	+22.2	+32.4	-10.7	+21.1	+23.6
α NMe _{ax}	-3.7	+19.3	+28.4			
β NMe _{eq}	-3.6	+0.3	-0.7	+1.8	-1.9	0
β NMe _{ax}	-3.6	-14.9	-6.4			

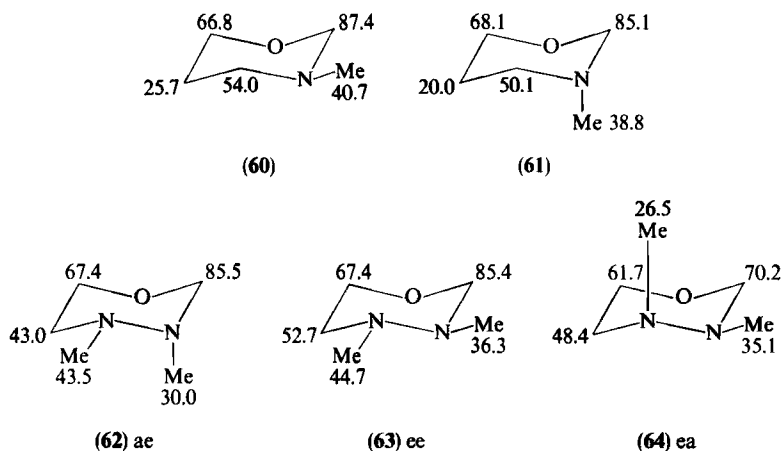
these parameters gives predicted chemical shifts for the eee and eae conformers **58** and **59**.⁹⁶



In a similar way, consideration of the ¹³C-NMR chemical shifts for the *N*-methyltetrahydro-1,3-oxazine conformers **60** and **61**⁹⁷ along with the

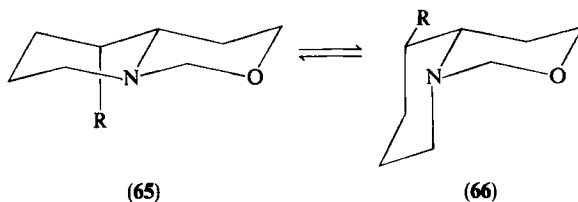
⁹⁶ A. R. Katritzky and R. C. Patel, *J. C. S. Perkin II*, 984 (1979).

⁹⁷ A. R. Katritzky, V. J. Baker, and F. M. S. Brito-Palma, *J. C. S. Perkin II*, 1739 (1980).



shifts in Table VIII enables the shift for the ae (62), ee (63), and ea (64) conformers of 3,4-dimethyltetrahydro-1,3,4-oxadiazine (Section III,F,2) to be estimated.⁹⁸

b. *Coupling Constant.* The magnitude of $J_{13\text{C-H}}$ in $N\text{-CH}$ systems varies with the orientation of the nitrogen lone pair with respect to the CH bond⁹⁹ being smaller for anti-periplanar than for synclinal arrangements.¹⁰⁰ Although direct measurement of the coupling constant from the spectra is subject to a large experimental error, it is found that the difference between the relevant $N\text{-}^{13}\text{CH}$ couplings for *cis*- and *trans*-quinolizidine is $\sim 6\text{--}9$ Hz.¹⁰⁰



For perhydropyrido[1,2-*c*][1,3]oxazine ($65 \rightleftharpoons 66$; R = H; existing as $\sim 90\%$ 65) the $J_{13\text{C-I-H}}$ values are 144 and 155 Hz, which become 150 and 155 Hz for the *cis*(4a-*H*, 5-*H*)-5-methyl derivative (existing as $\sim 50\%$ 65; R = Me \rightleftharpoons $\sim 50\%$ 66; R = Me).

⁹⁸ A. R. Katritzky, R. C. Patel, F. M. S. Brito-Palma, F. G. Riddell, and E. S. Turner, *Isr. J. Chem.* **20**, 150 (1980).

⁹⁹ W. B. Jennings, D. R. Boyd, C. G. Watson, E. D. Becker, R. B. Bradley, and D. M. Jerina, *J. Am. Chem. Soc.* **94**, 8501 (1972).

¹⁰⁰ G. Van Binst and D. Tourwé, *Heterocycles* **1**, 257 (1973).

In the anancomeric thiazine derivatives (shown in Table V), however, the trans-fused compound shows two equal couplings of 145 Hz and the cis-fused compound two equal couplings of 149 Hz.¹⁰¹ These results and others¹⁰² suggest caution in the use of this parameter in conformational assignments.

5. Inversion Barriers by Dynamic NMR Spectroscopy

Rate process with activation energies between ~ 6 and 25 kcal mol^{-1} can be studied conveniently by the NMR method. Line shape theories have been well reviewed.¹⁰³ In most cases a single rate constant k is estimated at the coalescence temperature, and ΔG^\ddagger is obtained from the Eyring equation. For exchange between two unequally populated sites, ΔG^\ddagger for the forward and reverse reactions are different. This is an important point to be considered in the case of nitrogen inversion phenomena.

A fundamental point arises in the interpretation of NMR coalescence data.² The rate constant obtained from an NMR experiment is always the sum of the forward and reverse rate constants, but three cases can be distinguished:

(i) If the process being observed is the freezing out of a biased equilibrium where K is, say, > 10 , the observed rate constant is effectively the greater of the forward and reverse rate constants and therefore corresponds to the change from least stable conformer \rightarrow transition state (although the activation energies thus derived have often erroneously been referred to ground states, i.e., to the more stable conformer). This applies in all applications of dynamic ^{13}C -NMR line broadening, including the use of the Anet equations.

(ii) If there are appreciable concentrations of both of the two conformers for the equilibration being observed, the individual activation energies can be obtained from the average ΔG^\ddagger measured and the ΔG° for the system using the equations derived by Bovey *et al.*¹⁰⁴

(iii) If the equilibrium under study is between two identical (or mirror image) conformers, then the measured rate constant is that for ground state \rightarrow transition state, and this applies regardless of the possible occurrence of minor amounts of other conformers along the reaction coordinate.

¹⁰¹ T. A. Crabb and P. A. Jupp, and Y. Takeuchi, *Org. Magn. Reson.* **20**, 239 (1982).

¹⁰² P. J. Chivers, T. A. Crabb, and Y. Takeuchi, *J. C. S. Perkin II*, 51 (1975).

¹⁰³ G. Binsch and H. Kessler, *Angew. Chem., Int. Ed. Engl.* **19**, 411 (1980); J. Sandström, "Dynamic NMR Spectroscopy". Academic Press, New York, 1982.

¹⁰⁴ F. A. Bovey, E. W. Anderson, F. P. Hood, and R. L. Kornegay, *J. Chem. Phys.*, **40**, 3099 (1964).

Neglect of these three points has led to much confusion in the literature. It was therefore suggested² that all ΔG^\ddagger be referred to half barriers. It is clearly necessary to state which half barrier is under discussion.

For biased equilibria, Anet¹⁰⁵ developed a method of estimating k and the population of the least stable conformer from line-broadening measurements. This method uses the expression developed by Gutowsky and Holm¹⁰⁶ from the Bloch equations

$$v(\omega) \propto \frac{[(1 + \tau T_2^{-1})P + QR]}{P^2 + R^2}$$

where $v(\omega)$ is the intensity as a function of frequency ω for exchange between two uncoupled sites of unequal population

$$P = \tau[T_2^{-2} - [1/2(\omega_A + \omega_B) - \omega]^2 + 1/4(\omega_A + \omega_B)^2] + T_2^{-1}$$

$$Q = \tau[1/2(\omega_A + \omega_B) - \omega - 1/2(p_A - p_B)(\omega_A - \omega_B)]$$

$$R = [1/2(\omega_A + \omega_B) - \omega](1 + 2\tau T_2^{-1}) + 1/2(p_A - p_B)(\omega_A - \omega_B)$$

and

$$\tau = \tau_A \tau_B / (\tau_A + \tau_B)$$

In the above expressions, τ_A is the lifetime of nuclei in site A, and τ_B is the lifetime of nuclei in site B; ω_A and ω_B are the chemical shifts of sites A and B, respectively; p_A and p_B are the populations for each site; and T_2 is the natural linewidth. In fitting data to the equation, the rate constant is varied until the linewidth in the calculated spectrum matches that in the experimental spectrum.

In addition to the rate constant, the population of the minor form and the chemical shift difference between the axial and equatorial forms are also variables in these calculations. The chemical shift difference ($\omega_A - \omega_B$) between the exchanging sites can be accurately observed at low temperature.

In simulating the experimental spectrum, variation of the rate constant at constant equilibrium constant (assumed) is performed to obtain a maximum broadening. The equilibrium constant is then varied until this maximum broadening matches that observed experimentally. Thus both the rate constant and the equilibrium constant are obtained at the temperature of the maximum broadening.

Provided that the population of the minor form is small ($< 10\%$), the magnitude of the maximum broadening is found to be dependent only on the population of the minor form and the chemical shift difference between

¹⁰⁵ F. A. L. Anet and V. J. Basus, *J. Magn. Reson.* **32**, 339 (1978).

¹⁰⁶ H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.* **25**, 1228 (1956).

the exchanging sites. The maximum broadening can be expressed, to a good approximation, by a formula derived by Anet¹⁰⁵ from the Gutowsky and Holm¹⁰⁶ equations:

$$\nu(\frac{1}{2} \text{ max}) = P \times \Delta\nu$$

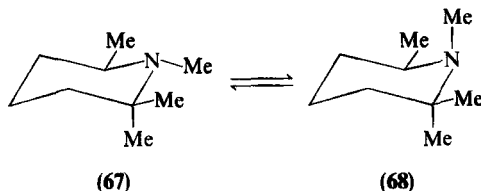
where $\nu(\frac{1}{2} \text{ max})$ is the magnitude of the maximum broadening at half-height of the signal in Hz, P is the population of the minor form, and $\Delta\nu$ is the chemical shift difference in Hz.

The rate constant at the temperature of maximum broadening was found to be virtually independent of the equilibrium constant but dependent on the chemical-shift difference between the exchanging sites according to the relationship

$$k = 2\pi \Delta\nu$$

where k is the rate constant at the temperature of maximum broadening from the minor to the major form in, sec^{-1} .¹⁰⁷

This dynamic NMR method, inapplicable to *N*-methylpiperidine itself because of the excessively great bias in the equilibrium, was applied to 1,2,2,6-tetramethylpiperidine.¹⁰⁸ This was selected because an equatorial methyl vicinal to *N*-methyl was expected¹⁰⁹ to lower the free energy difference (and incidentally raise the N inversion barrier) and thus bring the system into the dynamic NMR realm. In this system, only the two conformations **67** and **68** should be important. No ¹H spectral changes were observed in the range 34 to -150°C , but ¹³C-NMR broadening in the C-3 and C-5 signals (changing γ -effect **67** \rightarrow **68**) and in C-2 methyl(ax) (changing γ -effect **67** \rightarrow **68**) are noted in the region -30 to -90°C . Broadening was greatest at -60°C and for the C-2 methyl(ax) was 4 Hz greater than sharp lines of spectra. The C-2 methyl(ax) is subject to an additional γ -effect in **67** relative to **68**, and assuming this amounts to ~ 5 ppm, this may be equated to $\Delta\nu$ for substitution in the Anet equation. This gave ΔG^\ddagger (**68** \rightarrow **67**) 9.1 ± 0.3 kcal mol^{-1} , ΔG^\ddagger (**67** \rightarrow **68**) 11.0 ± 0.3 kcal mol^{-1} , and ΔG° 1.9 ± 0.2 kcal mol^{-1} at -60°C .



¹⁰⁷ Taken from I. Yavari, Ph.D. Thesis (1977). University of California, Los Angeles.

¹⁰⁸ F. A. L. Anet, I. Yavari, I. J. Ferguson, A. R. Katritzky, M. Moreno-Mañanas, and M. J. T. Robinson, *Chem. Commun.*, 399 (1976).

¹⁰⁹ R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and R. Scattergood, *J. C. S. Perkin II*, 406 (1974).

In the study of many conformational equilibria by variable-temperature ^{13}C -NMR spectroscopy, the signals for both conformers are not always observed, although line-broadening effects may be measured. As in the 1,2,2,6-tetramethylpiperidine equilibrium $67 \rightleftharpoons 68$ discussed above, some estimation of $\Delta\nu$ must be made in order to apply Anet's equations. Use may then be made of the substituent effects of the type shown in Table VIII (Section II,B,4). For example, the ^{13}C -NMR shifts for the C-2-Me in the eee and eae conformers of 1,2,4-trimethyltetrahydro-1,2,4-triazines (Section III,F,3), calculated from the shifts shown in Table VIII as δ 41.1 and δ 28.3, respectively, give a $\Delta\nu$ of 12.8 ppm, which together with the observed line broadenings gives $\Delta G_{\text{eee} \rightarrow \text{eae}}^\ddagger$ $11.4 \pm 0.2 \text{ kcal mol}^{-1}$ at -99°C and ΔG_{-99}° $1.20 \pm 0.1 \text{ kcal mol}^{-1}$ in favor of the eae conformer.⁹⁶

Note that ^{13}C - is better than ^1H -NMR because separations (in Hz) are greater; therefore broadenings are greater and the first Anet equation comes into play. Often broadenings are negligible or very small in ^1H -NMR spectra.

6. NMR Paramagnetic Shifts

By studying paramagnetic shifts of the α -methylene protons in substituted piperidines induced by nickel and cobalt acetylacetonates¹¹⁰⁻¹¹¹ and assuming that the contact shifts $\Delta\nu_{\text{eq}}$ and $\Delta\nu_{\text{ax}}$ in an equatorial lone-pair piperidine and $\Delta\nu_{\text{eq}}$ in an axial lone-pair piperidine are equal (same geometry with respect to lone pair) the equilibrium in 3- and 4-methylpiperidines was found to favor 88% lone-pair equatorial. However, cobalt acetylacetonate-induced shifts in the phenyl protons in N-substituted 4-phenylpiperidines showed differential complexation of equatorial and axial lone pairs,¹¹² so that the results¹¹⁰⁻¹¹¹ indicating NH axial preference are invalidated by not considering differential complexing of equilibrating species.

7. ^{15}N -NMR Spectroscopy

The existence of a linear correlation between ^{15}N shifts of piperidine derivatives with predominantly axial N-H bonds and those with predominantly equatorial N-H bonds and the ^{13}C shifts of hydrocarbon analogs showed that, whereas ^{15}N chemical shifts of N-methylpiperidines depend on the configuration of the N-substituent, those of N-H-substituted piperidines

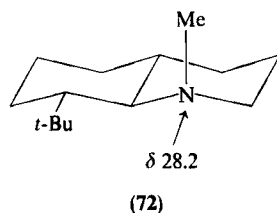
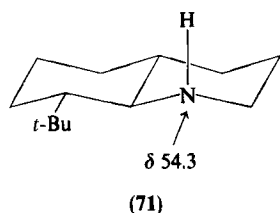
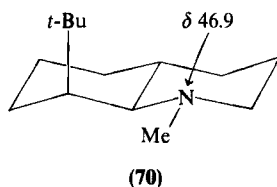
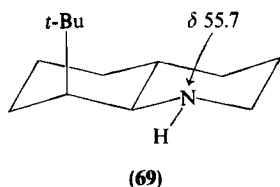
¹¹⁰ T. Yonezawa, I. Morishima, and Y. Ohmori, *J. Am. Chem. Soc.* **92**, 1267 (1970).

^{110a} I. Morishima, K. Okada, M. Ohashi, and T. Yonezawa, *Chem. Commun.*, 33 (1971).

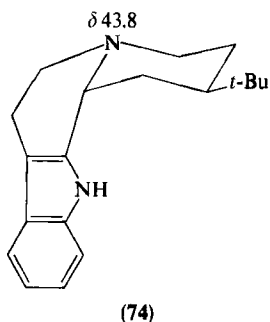
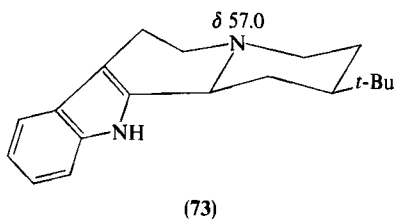
¹¹¹ I. Morishima, K. Okada, T. Yonezawa, and K. Goto, *J. Am. Chem. Soc.* **93**, 3922 (1971).

¹¹² I. D. Blackburne, A. R. Katritzky, and Y. Takeuchi, *J. Am. Chem. Soc.* **96**, 682 (1974).

do not.¹¹³ This has been confirmed by work on the *trans*-decahydroquinolines (69–72) (double chair conformation shown by X-ray crystallography).^{113a} Thus the ¹⁵N shift is of no value in determining *N*-H orientation in these types of compounds.¹¹⁴



The nature of the ring fusion in quinolizidine derivatives may be determined from the ¹⁵N chemical shifts, which are to lower field in the *trans*-fused derivatives. This is shown for the indolo[*a*]quinolizidines 73 and 74 (chemical shifts to low field of external anhydrous liquid ammonia)¹¹⁵ and by the perhydropyrido[1,2-*c*][1,3]thiazines: δ 66.9 *trans* conformer 312, δ 43.9 *S*-inside *cis* conformer 313.^{115a}



¹¹³ R. O. Duthaler, K. L. Williamson, D. D. Giannini, W. H. Bearden, and J. D. Roberts, *J. Am. Chem. Soc.* **99**, 8406 (1977).

^{113a} K. D. Hargrave and E. L. Eliel, *Isr. J. Chem.* **20**, 127 (1980).

¹¹⁴ G. T. Furst, R. L. Lichter, and F. W. Vierhapper, *J. Org. Chem.* **45**, 1521 (1980).

¹¹⁵ S. N. Y. Franso-Free, G. T. Furst, P. R. Srinivasan, R. L. Lichter, R. B. Nelson, J. A. Panetta, and G. W. Gribble, *J. Am. Chem. Soc.* **101**, 1549 (1979).

^{115a} Y. Takeuchi and T. A. Crabb, *Org. Magn. Reson.* **21**, 203 (1983).

C. KERR-CONSTANT MEASUREMENTS

The Kerr constant is related to the difference between the refractive indices of the medium parallel and perpendicular to an applied field, and these may be calculated for the assumed conformations. On this basis a 50:50 $N\text{-Me}_{\text{ax}} \rightleftharpoons N\text{-Me}_{\text{eq}}$ equilibrium was estimated for *N*-methylpiperidine and an $\sim 80\%$ $N\text{-H}_{\text{ax}}$ preference for piperidine in benzene solution.¹¹⁶ Some theoretical support¹¹⁷ was produced for this latter preference in terms of a more effective overall electron bonding in the $N\text{-H}_{\text{ax}}$ conformer. These results are very much out of line with those estimates based on other methods and the Kerr-constant work has been criticized³ on the grounds of insufficient accuracy in the bond polarizabilities used in the calculations.¹¹⁸

D. DIPOLE-MOMENT MEASUREMENTS

One of the present authors has extensively used the dipole-moment method to calculate conformational equilibria of saturated heterocycles. In hindsight this has been a frustrating experience: not so much because of the assumptions and approximations that must be made, but because the results in some cases are in good agreement with those derived from other methods, whereas for other groups of compounds the dipole-moment conclusions are clearly incorrect. In this discussion we first discuss the method, using piperidines as an example, and then attempt to assess its areas of applicability and causes of failure.

1. *The Method*

A general account of dipole-moment measurements and the use of these in conformational analysis has been given.³ At the University of East Anglia, for a study of the conformational equilibria of piperidines,¹¹⁹⁻¹²¹ electronic polarizations were estimated from tabulated bond polarizations¹²² (neglecting contributions of atomic polarization to the total polarization) or determined from refractive-index measurements. Most measurements were carried out in benzene or cyclohexane.

¹¹⁶ M. Aroney and R. J. W. LeFèvre, *J. Chem. Soc.*, 3002 (1958).

¹¹⁷ T. A. Claxton, *Chem. Ind. (London)*, 1713 (1964).

¹¹⁸ R. F. Zürcher, *J. Chem. Phys.* **37**, 2421 (1962).

¹¹⁹ R. J. Bishop, L. E. Sutton, D. Dineen, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc. B*, 493 (1967).

¹²⁰ J.-L. Imbach, R. A. Y. Jones, A. R. Katritzky, and R. J. Wyatt, *J. Chem. Soc. B*, 499 (1967).

¹²¹ R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, K. A. F. Record, and B. B. Shapiro, *J. Chem. Soc. B*, 1302 (1971).

¹²² R. J. W. Le Fèvre and K. D. Steel, *Chem. Ind. (London)* 670 (1961).

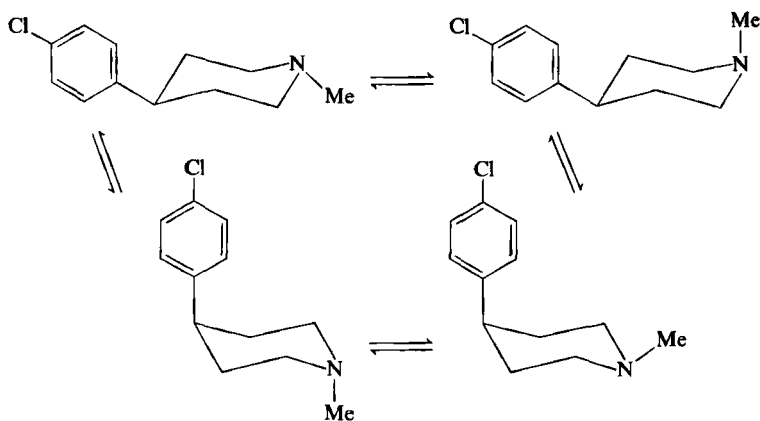
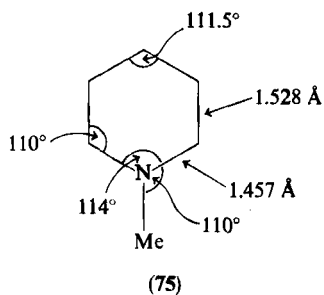


FIG. 6. Conformational equilibrium in 4-*p*-chlorophenyl-1-methylpiperidine.

The *N*-methylpiperidine equilibrium was investigated,¹¹⁹⁻¹²³ using the 4- (*p*-chlorophenyl) substituent as a conformational holding group (see Fig. 6), the proportion of the axial aryl conformers being estimated from the conformational free energy of the phenyl group in cyclohexane.³ Chair geometry was assumed for the piperidine ring, and the ring geometry was calculated from data shown in 75.¹¹⁹ The angle between the phenyl group axis and the C-3—C-4—C-5 ring plane was calculated as 111.5° and the moment of *N*-methylpiperidine was assumed to be equally inclined to the *N*-Me and the C-2—N and C-6—N bonds. The 4-aryl substituent was assumed not to alter the *N*-Me equilibrium from that in *N*-methylpiperidine. The moments of the conformers were estimated as the vector sum of the moments of *N*-methylpiperidine and of *p*-chlorophenylcyclohexane or by considering replacement of the *p*-position hydrogen in 4-phenylpiperidine by chlorine.



¹²³ N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *Tetrahedron Lett.*, 3345 (1964); *J. Am. Chem. Soc.* **87**, 1232 (1965).

As a result of the measurements and from the expression

$$\mu_{\text{observed}}^2 = \sum_i N_i \mu_i^2$$

(where N_i is the mole fraction), ΔG° for the $N\text{-Me}_{\text{ax}} \rightleftharpoons N\text{-Me}_{\text{eq}}$ equilibrium was calculated as $-0.53 \text{ kcal mol}^{-1}$ (71% $N\text{-Me}_{\text{eq}}$) in benzene solution at 25°C .¹¹⁹ This value was later updated¹²⁴ to $\Delta G^\circ -0.65 \text{ kcal mol}^{-1}$

2. Assessment of Results

The values given in Table XI (Section III,A,1) for the *N*-methylpiperidine equilibria show that dipole-moment measurements with the associated assumptions consistently give rise to lower estimates of $-\Delta G^\circ$ than those from other methods.

In several other series, conclusions were reached that are now known to be seriously in error. These include: 1,2-dialkylhexahydropyridazines (Section III,C,2), 3-alkyltetrahydro-1,3-oxazines (Section III,D,1), 3-alkyltetrahydro-1,3-thiazines (Section III,D,2), and trialkylhexahydro-1,3,5-triazines (Section III,G,5).

However, in many other series results have been obtained that are compatible with those from other methods and that gave the dipole-moment method an appearance of general reliability now known to be unjustified. Such compatible results include spiropiperidines (Section III,A,4), tropanes (Section III,B,4), 2-alkyltetrahydro-1,2-oxazines (Section III,C,2), perhydropyrido[1,2-*c*][1,3]oxazines (Section III,D,1), perhydropyrido[1,2-*c*][1,3]thiazines (Section III,D,2), dialkylhexahydropyrimidines and perhydropyrido[1,2-*c*]pyrimidines (Section III,D,3), 5-alkyldihydro-1,3,5-dithiazines (Section III,G,3), 3,5-dialkyltetrahydro-1,3,5-thiadiazines (Section III,G,4) and, in part, 1,2,4,5-tetraalkylhexahydro-1,2,4,5-tetrazines (Section III,H,4) as well as piperidines, tetrahydro-1,3-oxazines, and tetrahydro-1,3-thiazines containing an *N*-H group.

There are many possible sources of error in the calculation of equilibrium from dipole moments. It is difficult to calculate accurately the moments of model compounds. As has been pointed out,¹²⁴ the carbon skeleton itself contributes to the moment, as shown by the different dipole moments of ethyl bromide (2.069 D) and *n*-hexyl bromide (2.156 D) and of axial and equatorial fluorocyclohexane (1.81 D and 2.11 D, respectively). For nonsymmetrical molecules in general, the estimation of the precise direction of a dipole moment is subject to considerable error.

The dipole moments of *N*-axial and *N*-equatorial methylpiperidine may not be equal because of differing hybridization changes at nitrogen.

¹²⁴ R. A. Y. Jones, A. R. Katritzky, A. C. Richards, and R. J. Wyatt, *J. Chem. Soc. B*, 122 (1970).

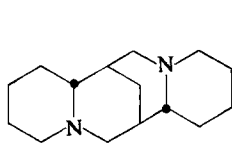
Dipole-dipole repulsions may invalidate the assumption that, e.g., the dipole moment of 4-(*p*-chlorophenyl)-1-methylpiperidine is the vector sum of that of *p*-chlorophenylcyclohexane and *N*-methylpiperidine.^{93,94} The assumption¹¹⁹ that the *N*-methylpiperidine moment is equally inclined to the *N*-Me and to the two N—C bonds may be invalid.¹²⁵

Such factors are particularly important when biased equilibria are considered.

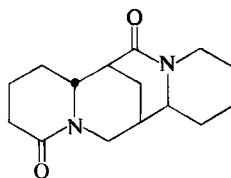
E. VIBRATIONAL SPECTROSCOPY

1. Bohlmann Region (2800–2600 cm^{-1}) of IR Spectra

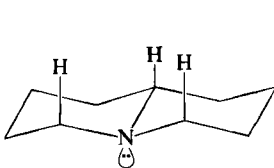
IR spectroscopy has been of considerable use in assigning the stereochemistry of quinolizidine natural products. Of the sparteine and related alkaloids, only molecules such as α -isosparteine (**76**), possessing a trans-fused quinolizidine system, exhibit a series of bands (Bohlmann bands) in the 2800–2600 cm^{-1} region of their IR spectra.¹²⁶ Compounds containing either a carbonyl group adjacent to the bridgehead nitrogen atom, as in 17-oxo-lupanine (**77**), or N-oxides give no such bands. The appearance of the bands is due to the C—H bonds α to the nitrogen atom, which are trans and axial with respect to the nitrogen lone pair. Two such bonds are usually necessary for the appearance of marked absorption: *trans*-quinolizidine (**78**) has three such C—H bonds, *cis*-quinolizidine (**79**) has only one. The IR



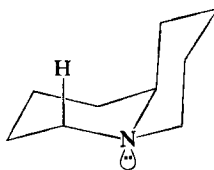
(76)



(77)



(78)



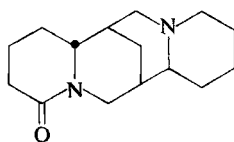
(79)

¹²⁵ P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *Tetrahedron* **33**, 915 (1977).

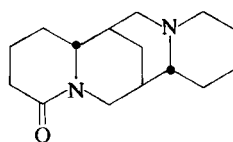
¹²⁶ F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958).

spectra of a series of deuterated quinolizidine and sparteine derivatives showed that the intensity of the bands approximately corresponded to the number of trans and axial α C—H bonds.

An attempt to put these findings on a quantitative basis was made by Wiewiorowski and Skolik.¹²⁷ The IR spectra of a number of alkaloids from the sparteine series were measured under identical conditions. 17-Oxolupanine (77), which has two amide groupings, was selected as an example of zero band formation and α -isoparteine (76) which has two *trans*-quinolizidine moieties, were selected as examples exhibiting maximum band formation. Two fundamental types of trans band were distinguished: the *cis*-[e.g., lupanine (80)] and the *trans*-quinolizidine types [e.g., α -isolupanine (81)]. The intensity of the trans band was expressed in terms of the integrated area of the peak, and, using this system, it was found that the trans band area for the *cis*-quinolizidine system was only 20% smaller than for the *trans*-quinolizidine system. The only compounds not showing any trans bands were dilactams and the majority of neutral salts. It was suggested¹²⁸ that the lower frequency of the trans bands compared with that of the normal C—H stretching vibrations could be due to a specific charge delocalization from the nitrogen lone pair to the α trans and axial C—H bonds. In *trans*-quinolizidine all three axial C—H bonds would participate in this type of charge delocalization. Because the axial C—H bonds on C-4 and C-6 have the same symmetry and force constants, vibrational coupling can occur. This gives rise to two bands in the IR spectrum of *trans*-quinolizidine, one at 2800 cm^{-1} due to the asymmetric stretching vibration and a stronger one at 2671 cm^{-1} due to the symmetric stretching. *cis*-Quinolizidine, which has only one α axial C—H bond, gives rise to a single band in the $2840\text{--}2600\text{ cm}^{-1}$ region.



(80)



(81)

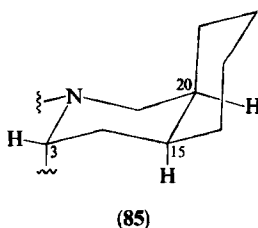
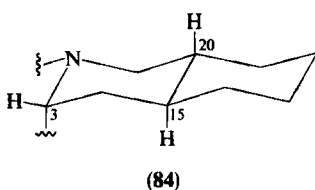
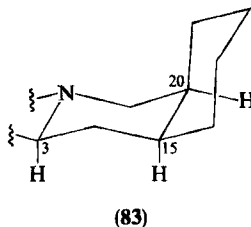
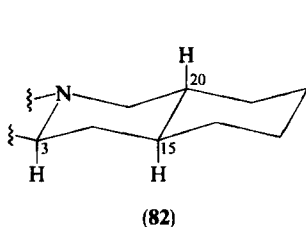
In summary, it was stated that for trans bands to occur in a given conformational of a heterocyclic system it is necessary to have one α axial C—H bond trans to the nitrogen lone pair. The intensity and complexity

¹²⁷ M. Wiewiorowski and J. Skolik, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **10**, 1 (1962).

¹²⁸ M. Wiewiorowski, J. Skolik, and P. J. Krueger, *Tetrahedron* **24**, 5439 (1968).

of the bands will be approximately proportional to the number of such bonds.¹²⁹

Similar correlations exist between the stereochemistry of yohimbines and related indole alkaloids and the appearance of bands in the $2800\text{--}2600\text{ cm}^{-1}$ region of their IR spectra.¹³⁰ All compounds possessing an α -hydrogen at C-3, i.e., normal (82) and allo (83) compounds, show two or more distinct and characteristic peaks of medium intensity on the low wave-number side of 2800 cm^{-1} in addition to the normal C—H stretching bands. Those compounds having a β -orientation of the C-3 hydrogen, i.e., pseudo (84) and epiallo (85) compounds such as ψ -yohimbine, (\pm)-epialloyohimbane, and 3-isoajmalicine, exhibit only shoulders on the low wave-number side of the main C—H band.



It was finally established^{131,132} that only those alkaloids possessing, in their preferred conformation(s), the C-3—H and at least one more adjacent C—H bond trans diaxial to the nitrogen lone pair will exhibit bands in their IR spectra between 2900 and 2700 cm^{-1} , one or more absorbing below 2800 cm^{-1} , whereas those alkaloids possessing in their preferred conformation(s) the C-3—H cis to the nitrogen lone pair will not.

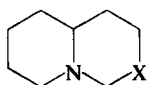
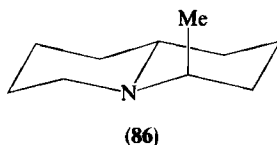
¹²⁹ M. Wiewiorowski, O. E. Edwards, and M. D. Bratek-Wiewiorowska, *Can. J. Chem.* **45**, 1447 (1967).

¹³⁰ E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.* **78**, 6417 (1956).

¹³¹ W. E. Rosen, *Tetrahedron Lett.*, 481 (1961).

¹³² W. F. Trager, C. M. Lee, and A. H. Beckett, *Tetrahedron* **23**, 365 (1967).

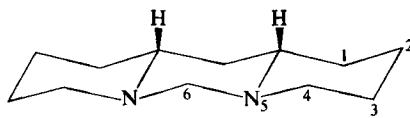
A study of isomeric monomethylquinolizidines revealed an apparent exception to the Bohlmann-bands criterion.^{133-134a} All the compounds adopted *trans*-fused conformations and all except the *trans*-(4-*H*,10-*H*)-4-methyl derivative **86** showed pronounced Bohlmann bands in their IR spectra. The 4-methyl derivative **86** gave rise to only one Bohlmann band at 2805 cm^{-1} . Thus the Bohlmann criterion should be applied to 4-substituted quinolizidines with care.



(87): X = O

(88): X = NR

(89): X = S



Bohlmann absorption is also characteristic of the *trans*-fused but not of the *cis*-fused conformations of the 1,3-heterocyclic systems **87**,¹³⁵ **88**,⁶⁵ and **89**.¹³⁶ Bohlmann bands are intense in the *trans-syn-trans*-perhydropyrido-[1,2-*c*:2',1'-*f*]pyrimidine **90**,¹³⁷ and these are markedly reduced in the 6,6-dideutero derivative,¹³⁸ showing the contribution of the interheteroatomic C-6—H_{ax} to the formation of Bohlmann bands in 1,3-heterocyclic systems.

Measurements of the Bohlmann bands in piperidine derivatives^{139,140} have supported a preference for *N*-H_{eq} in the piperidine equilibrium. The IR spectra of 2,6-dideuterated piperidine, *N*-methylpiperidine, and *N*-isopropylpiperidine showed two C—D absorptions at $2075\text{--}2030\text{ cm}^{-1}$ (anti-C—D

¹³³ T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc., London*, 218 (1961).

¹³⁴ T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

^{134a} C. D. Johnson, R. A. Y. Jones, A. R. Katritzky, C. R. Palmer, K. Schofield, and R. J. Wells, *J. Chem. Soc.*, 6797 (1965).

¹³⁵ T. A. Crabb and R. F. Newton, *Tetrahedron* **24**, 4423 (1968).

¹³⁶ T. A. Crabb and R. F. Newton, *Tetrahedron* **26**, 3941 (1970).

¹³⁷ P. J. Chivers and T. A. Crabb, *Tetrahedron* **26**, 3369 (1970).

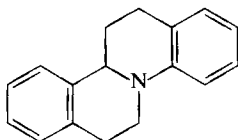
¹³⁸ P. J. Chivers and T. A. Crabb, unpublished observations; P. J. Chivers, Ph.D. Thesis, London (1970).

¹³⁹ T. Masamune and M. Takasugi, *Chem. Commun.*, 625 (1967).

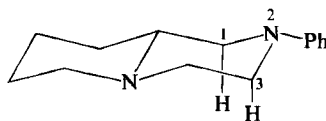
¹⁴⁰ M. Tsuda and Y. Kawazoe, *Chem. Pharm. Bull.* **16**, 702 (1968).

bond) and $2170\text{--}2150\text{ cm}^{-1}$ (gauche-C—D bond). On the basis of assumptions that *N*-isopropylpiperidine is exclusively *N*-equatorially substituted and that the intensity ratio of the two bands for this derivative is applicable to piperidine and *N*-methylpiperidine, ΔG° values (CCl_4 solution) for the $N\text{-R}_{\text{eq}} \rightleftharpoons N\text{-R}_{\text{ax}}$ equilibrium were estimated as $1.61\text{ kcal mol}^{-1}$ for *N*-methylpiperidine and $0.47\text{ kcal mol}^{-1}$ for piperidine.¹⁴⁰ Bohlmann bands have also been used in the assessment of the conformational equilibrium in decahydroquinolines.⁴³

Attachment of an aromatic ring to the nitrogen atom also markedly affects the formation of Bohlmann bands in those conformers permitting overlap of the nitrogen lone pair and the aryl ring orbitals. Thus trans-fused dibenzo[*a,f*]quinolizidine (**91**) does not exhibit Bohlmann bands.⁵¹ The strong Bohlmann absorption (2815 and 2770 cm^{-1}) in the IR spectrum of perhydropyrido[1,2-*a*]pyrazine (**92**) is only slightly reduced in that of the 3,3-dideuterated derivative, showing the very weak Bohlmann absorption arising from C-1—H_{ax} and C-3—H_{ax}.⁶⁷



(91)



(92)

2. Analysis of N-H Overtones¹⁴¹

In the gas-phase IR spectrum of piperidine, two bands with Q-branch maxima at 6577 and 6499 cm^{-1} occur, corresponding to first overtone *N*-H stretching frequencies. Because stretching frequencies of equatorial substituents are usually higher than those of axial substituents, it seemed probable that the more intense 6577 cm^{-1} band arose from the *N*-H equatorial conformer **93**. Support for this assignment came from a detailed study of the PQR band shapes (Fig. 7).

From the geometrical similarity between piperidine and cyclohexane it may be assumed that the *N*-H vibration causing the dipole change in **94** is parallel to the major axis of rotation (largest moment of inertia I_c) and accordingly the Q branch should be strong and the P and R bands, weak (parallel-type band). On the other hand the *N*-H equatorial bond in **93** has $\sim 28\%$ parallel character (*N*-H bond 111° to I_c), and P, Q, and R bands of

¹⁴¹ R. W. Baldock and A. R. Katritzky, *Tetrahedron Lett.*, 1159 (1968); *J. Chem. Soc. B*, 1470 (1968).

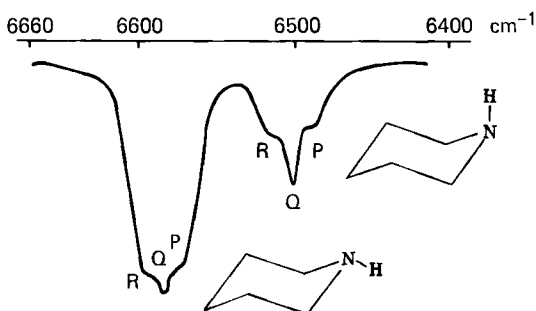
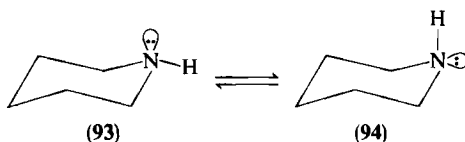


FIG. 7. Partial IR spectrum of gaseous piperidine at 90°C.¹⁴¹

approximately equal strength should be observed. Calculations based on the PR separation and the relative intensity of the Q branch support the assignments made on empirical grounds.



If A_{93} and A_{94} denote the band absorbance for the N -H equatorial and axial conformers **93** and **94** and ϵ are the corresponding extinction coefficients, then

$$x = A_{93}/A_{94} = (\epsilon_{93}/\epsilon_{94}) \cdot K_{93 \rightleftharpoons 94}$$

$$x = (\epsilon_{93}/\epsilon_{94})e^{-\Delta G/RT} = (\epsilon_{93}/\epsilon_{94})e^{-(\Delta H - T\Delta S)/RT}$$

$$\ln x = \ln \epsilon_{93}/\epsilon_{94} + \Delta S/R - \Delta H/RT$$

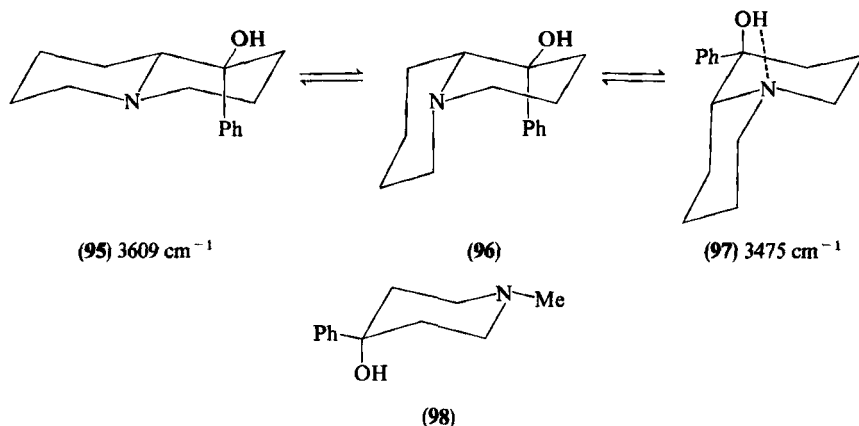
Then a plot of $\ln x$ against $1/T$ has a slope of $-\Delta H/R$. In fact, the temperature dependence of the spectra gave a ΔH of 0.5 ± 0.1 kcal mol⁻¹ for the equilibrium **93** \rightleftharpoons **94** (i.e., favoring N -H_{eq}) (ΔG values are considered to vary little from ΔH values). For dilute solution in CCl₄, ΔH was found to be $\sim 0.6 \pm 0.2$ kcal mol⁻¹ in favor of N -H_{eq}.¹⁴¹

The IR spectrum of piperidine in carbon tetrachloride shows a main N -H fundamental band at 3343 cm⁻¹ and a shoulder at 3315 cm⁻¹. It was argued that in the N -H_{eq} conformation partial delocalization of the nitrogen lone pair into the C—N bond occurs (decrease in N-atom charge density) with resulting increase in the N -H stretching frequency, and accordingly the main band was assigned to the N -H_{eq} conformation. Analysis of these overlapping bands gives ΔH 0.40 kcal mol⁻¹ in favor of N -H_{eq}.¹⁴²

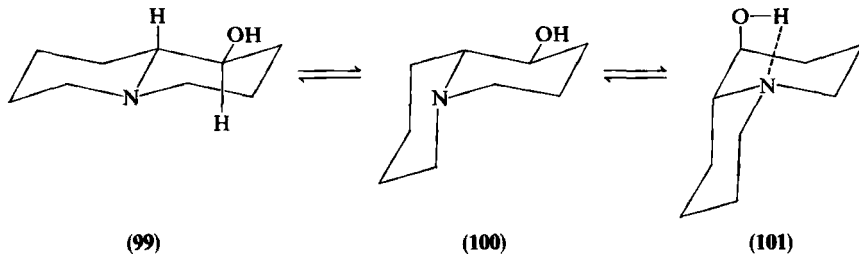
¹⁴² P. J. Krueger and J. Jan, *Can. J. Chem.* **48**, 3236 (1970).

3. H-Bonding Studies

The position of conformational equilibrium in OH-substituted heterocycles may be estimated by IR H-bonding studies.^{142a} For example, for the equilibrium $95 \rightleftharpoons 96 \rightleftharpoons 97$, two bands at 3609 cm^{-1} (free OH) and 3475 cm^{-1} (intramolecular H-bonded OH) are observed. The % trans-fused conformer (60%) was calculated by comparison of the integrated area of the 3609 cm^{-1} band with that of the model compound **98**.¹⁴³

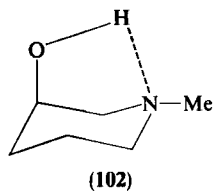


A value of ΔG° for the quinolizidine equilibrium was obtained by IR spectroscopic techniques. Dilute solution measurements (0.006 M CCl_4) in 10-cm cells on *trans*-(1-*H*,9*a*-*H*)-1-hydroxyquinolizidine ($99 \rightleftharpoons 100 \rightleftharpoons 101$) showed a small band at 3250 cm^{-1} corresponding to the H-bonded *cis*-fused conformer **101**. The epimeric *cis*-(1-*H*,9*a*-*H*) compound was taken as a 100% H-bonded model, and the concentration of the *cis*-fused conformer **101** was then deduced. A correction must be made for the presence of **100**, which was estimated by studies on the conformational equilibrium in 1-methyl-3-



^{142a} H. S. Aaron, *Top. Stereochem.* **11**, 1 (1979).

¹⁴³ H. S. Aaron and C. P. Ferguson, *Tetrahedron Lett.*, 6191 (1968).



hydroxypiperidine (102). By this means ΔG° was estimated for the *cis* \rightleftharpoons *trans*-quinolizidine equilibrium as $-2.6 \text{ kcal mol}^{-1}$.¹⁴³

F. MICROWAVE SPECTROSCOPY

Analysis of the microwave spectrum of piperidine and of *N*-deuteropiperidine suggests that the strongest Q-branch series together with the associated R-branch lines arise from the *N*-H-axial conformer.¹⁴⁴ From this absorption and from a weaker series of Q branches, $I_{\text{eq}}/I_{\text{ax}}$ (the relative intensities of the type-A lines of *N*-H_{eq} and *N*-H_{ax} conformers corrected for the frequency factor) was estimated as $\sim 1/6$ at -34°C . This ratio is related to $\Delta E = E_{N-H_{\text{ax}}} - E_{N-H_{\text{eq}}}$ by the expression

$$I_{\text{ax}}/I_{\text{eq}} = (\mu_a^{\text{ax}}/\mu_a^{\text{eq}})^2 e^{-\Delta E/kT}$$

Values of μ_c^{ax} and μ_c^{eq} were obtained from the linear Stark effects, and, making the assumption that the total dipole moment of both conformers is the same, then $\mu_a^{\text{ax}}/\mu_a^{\text{eq}}$ was estimated. Substitution in the equation gave $\Delta E = 245 \pm 150 \text{ cal mol}^{-1}$ corresponding to 60% *N*-H_{eq} conformer at 20°C .¹⁴⁴ The validity of the assumption of equal overall dipole moments of the two conformers has been challenged.⁹

G. PHOTOELECTRON SPECTROSCOPY

Photoelectron spectroscopy¹⁴⁵ has been particularly useful in the conformational analysis of heterocyclic molecules possessing vicinal electron lone pairs, especially in the hexahydropyridazine system.^{12,145a} In such a system the two lone-pair orbitals on nitrogen do not ionize at the same potential because of interactions with each other and with other orbitals. Lone-pair–lone-pair interactions are expected to dominate and are dependent upon the

¹⁴⁴ P. J. Buckley, C. C. Costain, and J. E. Parkin, *Chem. Commun.*, 668 (1968).

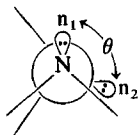
¹⁴⁵ For a review, see S. D. Worley, *Chem. Rev.* **71**, 295 (1971).

^{145a} S. F. Nelsen, *Acc. Chem. Res.* **14**, 131 (1981).

dihedral angle θ between the lone pairs.¹⁴⁶⁻¹⁴⁸ Extensive work on acyclic and cyclic hydrazine derivatives¹⁴⁶⁻¹⁵⁴ showed that the difference Δ between the first two ionization potentials varied with θ , and relationships were proposed.^{149,151} For example, if the interaction between the lone pairs n_1 and n_2 shown in **103** is largely determined by the dihedral angle θ , then the relationship between the splitting of the two molecular orbitals $n_+ = (n_1 + n_2)/\sqrt{2}$ and $n_- = (n_1 - n_2)/\sqrt{2}$ may be expressed as

$$\Delta E = E_{n_-} - E_{n_+} = A \cos \theta + B$$

Studies on compounds of known conformation permit a determination of $A = 2.20$ eV and $B = -0.15$ eV. (Values of 2.3 eV and a minimum of 0.5 eV for $\theta = 180^\circ$ and 90° , respectively, have also been suggested.)



(103)

The observed vertical ionization potentials then give the negative values of E_{n_-} and E_{n_+} , using Koopmans's approximation.¹⁵⁵ (Deviations¹⁵² from such relationships may arise from the approximation of taking the energy separation between the two highest occupied molecular orbitals as that between the symmetric and antisymmetric lone-pair orbital combinations because there is significant mixing with the hydrocarbon portion of the molecule.¹⁵⁶)

Such relationships have permitted conformational assignments to be made to a variety of hexahydropyridazines. Thus 1,2-dimethylhexahydropyridazine (**104**) shows a pair of peaks ($\Delta E -2.32$) corresponding (in the vapor phase) to **105** ($\theta = 170^\circ$) and a pair ($\Delta E 0.77$ eV) corresponding to **106** or **107** ($\theta = 65^\circ$) with **105** predominating.^{147,149,152}

¹⁴⁶ S. F. Nelsen and J. M. Buschek, *J. Am. Chem. Soc.* **95**, 2011 (1973).

¹⁴⁷ S. F. Nelsen, J. M. Buschek, and P. J. Hintz, *J. Am. Chem. Soc.* **95**, 2013 (1973).

¹⁴⁸ P. Rademacher, *Angew Chem.* **85**, 410 (1973).

¹⁴⁹ P. Rademacher, *Tetrahedron Lett.*, 83 (1974).

¹⁵⁰ S. F. Nelsen and J. M. Buschek, *J. Am. Chem. Soc.* **96**, 2392 (1974).

¹⁵¹ S. F. Nelsen and J. M. Buschek, *J. Am. Chem. Soc.* **96**, 6982 (1974).

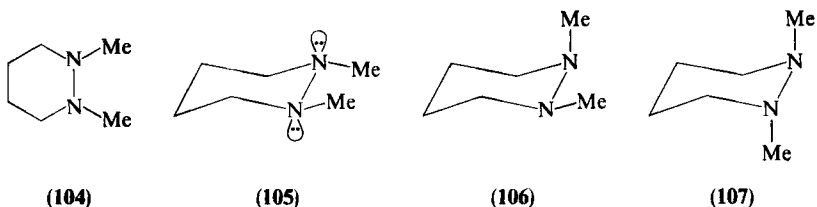
¹⁵² S. F. Nelsen and J. M. Buschek, *J. Am. Chem. Soc.* **96**, 6987 (1974).

¹⁵³ P. Rademacher, *Chem. Ber.* **108**, 1548 (1975).

¹⁵⁴ P. Rademacher and H. Koopmann, *Chem. Ber.* **108**, 1557 (1975).

¹⁵⁵ T. Koopmans, *Physica (Amsterdam)* **1**, 104 (1934).

¹⁵⁶ Note 6 in Ref. 149 (communication from Professor J. P. Syder).



One advantage of the photoelectron method is that it gives an estimate of the position of conformational equilibrium for those systems undergoing fast interconversion on the NMR time scale. The estimation, however, cannot be quantitative.

H. CALORIMETRIC METHODS

The application of calorimetric methods to the determination of the position of conformational equilibria in reduced heterocyclic systems may be illustrated by reference to work¹⁵⁷ on the piperidine equilibrium. If ΔE and $\Delta E'$ represent the energy differences between the $N\text{-H}_{\text{ax}}$ and $N\text{-H}_{\text{eq}}$ piperidine conformers and between the chair and twist-boat conformations, respectively, then the partition coefficient Q for the complete conformational equilibria may be expressed as

$$Q = [1 + \exp(\Delta E/RT)][1 + 3 \exp(\Delta E'/RT)]$$

Consideration of the effects of anharmonicity involved two empirical constants Z and $\tilde{\nu}_{\text{anh}}$. Because only three quantities could be evaluated from the calorimetric data with any reliability, $\Delta E'$ was taken as $5.5 \text{ kcal mol}^{-1}$ (cf. cyclohexane³). Fitting of the thermodynamic data then gave $Z = 1.85 \text{ kcal mol}^{-1}$, $\tilde{\nu}_{\text{anh}} = 750 \text{ cm}^{-1}$ and $\Delta E = 0.57 \text{ kcal mol}^{-1}$, favoring the $N\text{-H}_{\text{eq}}$ conformer. Whereas ΔE was found to be insensitive to the value of $\Delta E'$, ΔE was shown to be sensitive to the experimental error in the calorimetrically determined value of the entropy.

I. ELECTROCHEMICAL METHODS

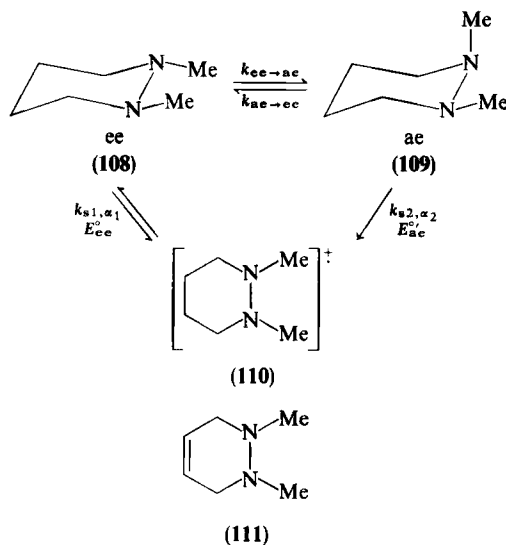
Early cyclic voltammetric (CV) studies^{158,159} established that tetraalkyl hydrazines give chemically reversible one-electron oxidations with no evi-

¹⁵⁷ D. W. Scott, *J. Chem. Thermodyn.* **3**, 649 (1971).

¹⁵⁸ S. F. Nelsen, V. Peacock, and G. R. Weisman, *J. Am. Chem. Soc.* **98**, 5269 (1976).

¹⁵⁹ S. F. Nelsen and P. J. Hintz, *J. Am. Chem. Soc.* **94**, 7108 (1972).

dence of radical-cation decay. Later work^{145a,160-162} on some six-membered-ring hydrazines at low temperature showed two oxidation waves. The oxidation of the ee hydrazine is rapid and nearly reversible in contrast to the slow and electrochemically irreversible oxidation of the ea hydrazine. Assuming the occurrence of the kinetic scheme $108 \rightleftharpoons 109 \rightleftharpoons 110$ (where E° , k_s , and α are the standard potential, standard heterogeneous electron-transfer rate constant, and electron-transfer coefficient for the respective electrode reactions), then digital simulation produced good fits to the observed CV curves. The simulation gives the equilibrium constant K ($[ee]/[ae]$) when ΔG^\ddagger for the ae and ee interconversions is $> 11 \text{ kcal mol}^{-1}$ (when the ratio of the two waves is scan-rate independent). For scan-rate dependent oxidation peak sizes, the simulation gives $K(k_{ce \rightarrow ae} + k_{ac \rightarrow ee})^{1/2}$.



For 1,2-dimethyltetrahydropyridazine (111), the NMR methods (see Section III,C,2) only detect the ae conformation, whereas CV enables ΔG° ($ee \rightleftharpoons ae$) to be estimated as almost certainly above 3 kcal mol^{-1} .¹⁶¹

Thus, low-temperature CV provides a complementary technique to the NMR method for the conformational analysis of cyclic hydrazines.

¹⁶⁰ S. F. Nelsen, L. Echegoyen, and D. H. Evans, *J. Am. Chem. Soc.* **97**, 3530 (1975).

¹⁶¹ S. F. Nelsen, L. Echegoyen, E. L. Clennan, D. H. Evans, and D. Corrigan, *J. Am. Chem. Soc.* **99**, 1130 (1977).

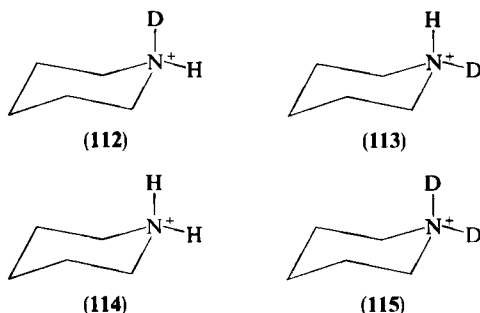
¹⁶² S. F. Nelsen, E. L. Clennan, and D. H. Evans, *J. Am. Chem. Soc.* **100**, 4012 (1978).

J. CHEMICAL METHODS

The fast chemical reaction method of studying conformational equilibria has been analyzed in detail.¹⁶³

1. Protonation (Deuteronation) Studies

In principle, the estimation of conformational equilibrium in a piperidine derivative by protonation is very simple. If nitrogen inversion is slow compared to deuteronation, if H^+/D^+ exchange does not occur in the salts, and if H^+/D^+ exchange is unimportant in the mixing process, then the relative proportion of the salts corresponds to that of the conformers. Thus the spectrum of pure dry *cis*-3,5-dimethylpiperidine in deuterotrifluoroacetic acid (unchanged after 2 days) showed a septet at δ 2.70 for the 2,6-axial protons in **112** and **113**. This was interpreted as a triplet for **112** and a quartet for **113** and analysis of the multiplets gave 54% **112** and 46% **113** ($\Delta G^\circ N-H_{eq} \rightleftharpoons N-H_{ax}$ 0.1 kcal mol⁻¹).¹⁶⁴



This work was criticized¹⁶⁵ because the time of mixing may be long compared to that of proton transfer and nitrogen inversion, but the validity of the original experiment has been defended by studies on model compounds.¹⁶⁶

Attention, however, has been drawn to the problem of H/D scrambling at the liquid-liquid interface.¹⁶⁷ In the spectrum of a solution obtained by extraction of *cis*-3,5-dimethylpiperidine from a dilute solution in cyclohexane with D₂SO₄, the triplets due to **112** show a clear additional coupling

¹⁶³ J. McKenna, *Tetrahedron* **30**, 1555 (1974).

¹⁶⁴ H. Booth, *Chem. Commun.*, 802 (1968).

¹⁶⁵ J. McKenna and J. M. McKenna, *J. Chem. Soc. B*, 644 (1969).

¹⁶⁶ H. Booth and J. H. Little, *J. C. S. Perkin II*, 1846 (1972).

¹⁶⁷ P. J. Crowley, G. A. Morris, and M. J. T. Robinson, *Tetrahedron Lett.*, 3575 (1976).

to $N\text{-H}_{\text{eq}}$, whereas the spectrum of *cis*-3,5-dimethylpiperidine in excess CF_3COOD (Booth's method) indicates the presence of all four ions **112**–**115**. It was concluded¹⁶⁷ that deuteration in the original experiment¹⁶⁴ could not have been under kinetic control.

However, it was found that the ratios of protonated ions are independent of acid (H_2SO_4) concentration when extraction from an inert solvent is used. Thus in the ^{14}N -decoupled spectrum of *cis*-3,5-dimethylpiperidine extracted from cyclohexane by D_2SO_4 the $N\text{-H}_{\text{ax}}/N\text{-H}_{\text{eq}}$ ratio was estimated from the areas of the $N\text{-H}$ proton signals to be 0.86 giving a ΔG_{20}° of $0.1 \text{ kcal mol}^{-1}$.¹⁶⁷ Similar kinetic-controlled protonation studies¹⁶⁸ (extraction by D_2SO_4 from cyclohexane solution) shows ΔG_{15}° $2.7 \pm 0.2 \text{ kcal mol}^{-1}$ for the *N*-methylpiperidine equilibrium. Significantly, it has been found¹⁶⁷ that the ratio of protonated ions varies when neat amine is mixed with varying concentrations of acids, invalidating the early estimate^{164,166} based on mixing of the amine with trifluoroacetic acid.

The kinetically controlled protonation method may also be applied to the determination of the conformational free energy of *C*-methyl groups in piperidines. For example, protonation of 1,5-dimethylpiperidine (in which ^{13}C is located in the $N\text{-CH}_3$ group) in dodecane and estimation of the ions produced by ^{13}C -NMR spectroscopy gives ΔG_{20}° of $1.5 \pm 0.1 \text{ kcal mol}^{-1}$ for the 3-methyl group.¹⁶⁹

2. Kinetics of Methylation

The kinetic method may be conveniently illustrated by reference to the methylation of the *trans* (2-*H*,9*a*-*H*)-2-methylquinolizidine (**116**) (Fig. 8) because this gives rise to an $\sim 50:50$ mixture of the two methiodides.^{134a}

The basic expression required for the analysis of this system is that worked out for conformationally mobile systems in general by Eliel and by Winstein and Holness.^{3,169a} If $c(1-x)$ and cx denote the concentrations of the *trans*-fused and *cis*-fused conformers of the methylquinolizidine at equilibrium,

$$K = x/(1-x)$$

The rates of formation of the *trans*-fused and *cis*-fused methiodides are given by

$$d[\text{trans}]/dt = c(1-x)k_1, \quad d[\text{cis}]/dt = cxk_c$$

¹⁶⁸ P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *Chem. Commun.*, 825 (1974).

¹⁶⁹ M. J. T. Robinson, *Chem. Commun.*, 844 (1975).

^{169a} J. I. Seeman, *Chem. Rev.* **83**, 83 (1983).

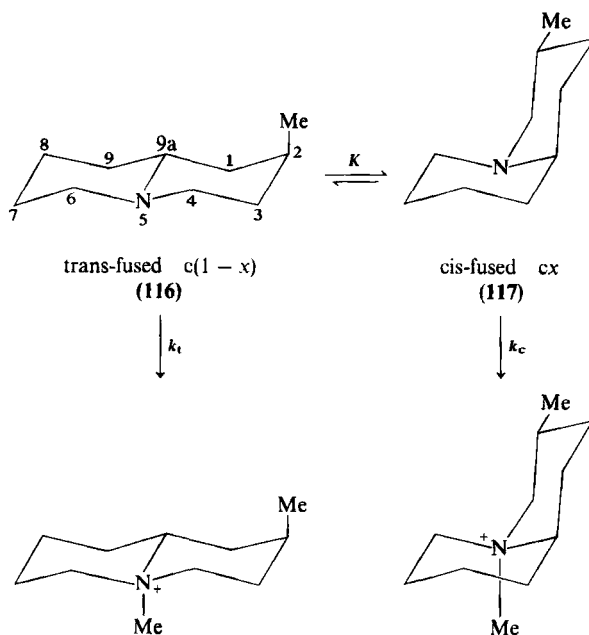


FIG. 8. Reaction between *trans*-(2-*H*, 9a-*H*)-2-methylquinolizidine and methyl iodide,^{134a} where K is the equilibrium constant for the $\text{trans} \rightleftharpoons \text{cis}$ equilibrium, k_t is the rate constant for methylation of *trans* conformer, and k_c is the rate constant for methylation of a *cis* conformer.

and the overall rate of methiodide formation then becomes

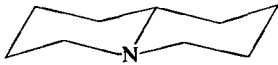
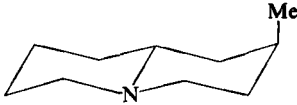
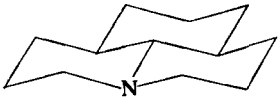
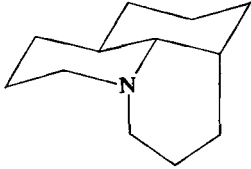
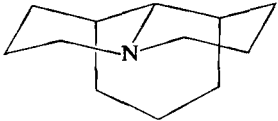
$$\frac{d[\text{trans}]}{dt} + \frac{d[\text{cis}]}{dt} = \frac{c}{1 + K} (k_t + k_c K) = kc$$

where k is the observed pseudo first-order rate constant for methiodide formation.

Values of k for the *trans*-(2-*H*, 9a-*H*)-2-methylquinolizidine, quinolizidine, and the locked hexahydrojulolidines are shown in Table IX, and this gives a K of 0.0087 (ΔG° at 25°C = 2.8 kcal mol⁻¹) for the *trans*-2-methylquinolizidine.

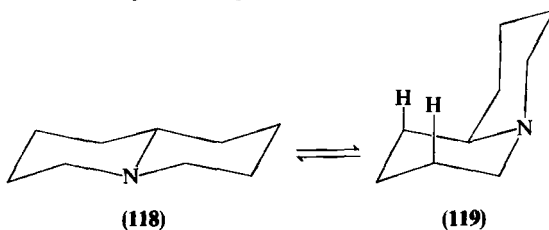
An attempt was made to extend this result to an estimation of K for the quinolizidine equilibrium. For the 2-methyl compound 116 discussed above, there is a difference of one gauche-butane (gb) interaction between the *cis*- and *trans*-fused conformers 116 and 117 compared with a difference of three such interactions between the quinolizidine conformers 118 and 119. This gives ΔG° at 25°C for quinolizidine as 2.8 + 2gb = 2.8 + 1.6 = 4.4 kcal mol⁻¹. This value is uncertain because even groups remote from

TABLE IX
PSEUDO FIRST-ORDER RATE CONSTANTS (k) FOR METHIODIDE
FORMATION IN ACETONITRILE SOLUTION^{134a}

Structure	k ($\times 10^{-4} \text{ sec}^{-1}$ at 24.5°C)
	64.2
	115
	63.6
	6151
	0.024 ^a

^a At 28.2°C.

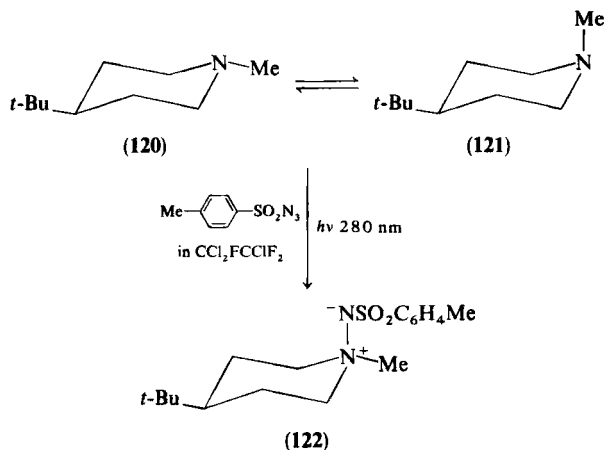
nitrogen may affect the rate of quaternization so that the use of the julolidines as models may not be permissible.^{134a}



3. Electrophilic Addition of Nitrenes to Tertiary Amines

p-Toluenesulfonylnitrene (*p*-MeC₆H₄SO₂N) shows lack of steric discrimination in its reaction, for example, with amines to form aminimides. It

appeared therefore to be a suitable conformational probe for the *N*-methylpiperidine equilibrium.¹⁶³ The reaction with 1-methyl-4-*tert*-butylpiperidine (**120** \rightleftharpoons **121**) gave only one aminimide (**122**) and it was deduced that the equilibrium mixture contains less than 1% of the *N*-Me_{ax} conformer **121** ($-\Delta G_{27}^0 \geq 2.7$ kcal mol⁻¹ in CCl₂FCClF₂).¹⁷⁰



K. ULTRASONIC MEASUREMENTS

The ultrasonic method (for general background, see Ref. 170a) has been used to study conformational equilibria in piperidines, piperazines, and morpholines. Ultrasonic relaxation arises as a result of perturbation of the conformational equilibrium by the sound wave. In anancomeric (i.e., with regard to ring inversion) derivatives such as 1,2,4,6-tetramethylpiperidine (**123** \rightleftharpoons **124**), the relaxation is a result of perturbation of the N-inversion process. The method provides ΔH^\ddagger , obtained from Eyring rate plots of $\log (T_t)^{-1}$ against T^{-1} , for the less stable **124** to the more stable conformation **123**. For the change between two sites **123** \rightleftharpoons **124** it was shown that when relaxation occurs,

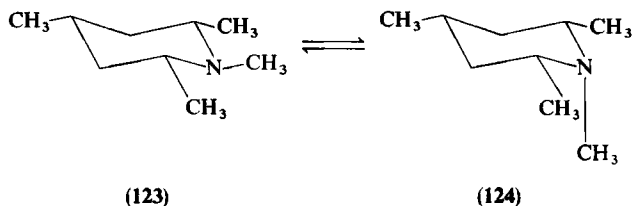
$$\alpha/f^2 = \frac{P_1(P_2)^{T_0/T}}{uT^2[P_4(P_3)^{T_0/T} + 4\pi^2 f^2] + B}$$

where α is the ultrasonic absorption, u the velocity, $P_2 = \exp[-(\Delta H^\circ + E)/RT_0]$, $P_3 = \exp(-E/RT_0)$, T_0 = a fixed temperature, chosen as 25°C, and

¹⁷⁰ D. C. Appleton, J. McKenna, J. M. McKenna, L. B. Sims, and A. R. Walley, *J. Am. Chem. Soc.* **98**, 292 (1976).

^{170a} E. Wyn-Jones and R. A. Pethrick, *Top. Stereochem.* **5**, 205 (1970).

where P_1 and P_4 are constants and B represents contribution to α/f^2 not related to the relaxation process of interest. The value for B is obtained at each temperature by extrapolating the values of α/f^2 to high frequency.



The value for P_3 was obtained from ΔH^\ddagger (from Eyring plots) because $E = \Delta H^\ddagger + RT$. ΔG° was taken as equal to ΔH° , and from literature values of ΔH° estimates of P_4 were obtained. The constants P_1 – P_4 were then derived from the experimental data and the foregoing equation.

For the 1,2,4,6-tetramethylpiperidine equilibrium $123 \rightleftharpoons 124$, $\Delta H^\circ = 1.0$ kcal mol⁻¹, and for the *N*-methylpiperidine equilibrium, $\Delta H^\circ = 0.88$ kcal mol⁻¹ and refer to measurements made on pure liquids. These values are much lower than those obtained by most other techniques (Table XI) and it is agreed² that values of ΔH° obtained by spectroscopic methods are more reliable than those from ultrasonic techniques. ΔH^\ddagger (axial \rightarrow transition state) values, however, are in agreement with those from other methods, and for *N*-methylpiperidine a value of 5.02 kcal mol⁻¹ has been obtained from Eyring plots and a value of 5.76 kcal mol⁻¹, using the foregoing equation.¹⁷¹

III. Results for Individual Ring Systems

A. MONOCYCLIC PIPERIDINES

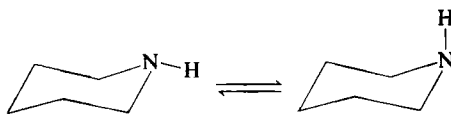
1. Conformational Equilibria of *N*-Substituents

a. *Piperidine*. Much of the work carried out on piperidine has been discussed in Section II to illustrate physical methods of examining conformational equilibria. A survey of the published work is shown in Table X. A review in 1975 concluded that piperidine was predominantly *N*-H equatorial with $\Delta G^\circ \sim 0.4$ kcal.¹ Since then this has been particularly supported by

¹⁷¹ V. M. Gittins, P. J. Heywood, and E. Wyn-Jones, *J. C. S. Perkin II*, 1642 (1975).

TABLE X

SUMMARY OF PUBLISHED WORK ON THE POSITION OF CONFORMATIONAL EQUILIBRIA IN PIPERIDINES



Phase	ΔG° (kcal mol ⁻¹) ^a	Method	Reference	Section of this review
—	—ve	Analogy with carbanions	21	—
—	—ve	Theory	117	—
Gas	+ve	Calculations	22	—
	-0.6 (ΔH°)	Calculations	23	—
CD ₃ OD	—ve	¹ H-NMR chemical shifts	37	II,B,1
CCl ₄	—ve	¹ H-NMR chemical shifts	172	—
CDCl ₃	-1.2 (24°C)	¹ H-NMR paramagnetic shifts	110, 111	II,B,6
CHFC1 ₂ :CHF ₂ Cl	+0.36 (25°C)	NMR (¹³ C and ¹ H)	173	This section
CCl ₄	+0.5 (23°C)	IR Bohlmann bands	139	II,E,1
CCl ₄	+0.47 (23°C)	IR C-D Bohlmann absorption	140	II,E,1
CCl ₄	+0.4 (ΔH°)	IR NH fundamental	142	II,E,2
Gas	+0.6	IR	157	II,E,2
Gas	+0.5 (ΔH°)	IR NH overtones	141	II,E,2
CCl ₄	+0.6 (ΔH°)	IR NH overtones	141	II,E,2
Gas	+0.2	Microwave	144	II,E,2
C ₆ H ₆	-0.8	Kerr constants	116	II,C
C ₆ H ₁₂	+0.4	Dipole moments	173a	II,D
CF ₃ COOD	+0.1	Protonation	164	II,H,1
Cyclohexane	0.00	Protonation	167	II,H,1

^a A positive value indicates that the NH equatorial conformer is favored.

work of Anet and Yavari¹⁷³ (see below). The paramagnetic-shift work¹¹⁰⁻¹¹¹ has been criticized¹¹² (Section II,B,6), and the resulting estimation of equilibrium may be ignored. The estimate³⁷ based on Δ_{ae} values may also be dropped because this parameter has been shown⁴³ to be insensitive to *N*-H orientation. The most convincing evidence for the *N*-H_{eq} predominance is

¹⁷² C. C. Price, *Tetrahedron Lett.*, 4527 (1971).

¹⁷³ F. A. L. Anet and I. Yavari, *J. Am. Chem. Soc.* **99**, 2794 (1977).

^{173a} R. A. Y. Jones, A. R. Katritzky, A. C. Richards, R. J. Wyatt, R. J. Bishop, and L. E. Sutton, *J. Chem. Soc. B*, 127 (1970).

provided by (i) the IR study of *N*-H overtones¹⁴¹ (see Section II,E,2) and (ii) the low temperature NMR study of piperidine.¹⁷³ At -172°C the proton-decoupled ^{13}C -NMR spectrum of carefully dried piperidine showed two absorptions for C-3 in the ratio 85:15 (ΔG° 0.36 kcal mol⁻¹). This gives a 65:35 population at 25°C . The triplet nature of the 2- H_{ax} proton signal in the ^1H -NMR spectrum of piperidine at temperatures below -140°C showed the predominant conformation of piperidine to be that with *N*- H_{eq} .

Photoelectron spectra and STO-3G calculations on methylpiperidines show that equatorial methyl substituents at the 2-, 3-, and 4-positions lower the ionization potential of the nitrogen lone pair by ≤ 0.1 eV. An axial methyl at C-2, however, lowers the ionization potential by ~ 0.26 eV. These influences on ionization potentials are nearly identical in both piperidines and *N*-methylpiperidines, indicating that the lone-pair orientations in both systems are similar. The STO-3G calculations indicate a favoring of the equatorial *N*-H conformation of the piperidines by 1.0–1.9 kcal mol⁻¹.¹⁷⁴

Line-shape analysis of the ^{13}C -NMR spectrum of piperidine gave ΔG^{\ddagger} 6.1 ± 0.2 kcal mol⁻¹ (-142°C) for the *N*- $\text{H}_{\text{eq}} \rightarrow \text{N}$ - H_{ax} inversion process.¹⁷³ $\Delta G^{\ddagger}_{65^{\circ}}$ for ring inversion of piperidine has been found to be -10.2 kcal mol⁻¹.³⁷

b. *N*-Alkylpiperidines. A survey of the published work on *N*-methylpiperidine is given in Table XI, and much of this has been discussed in detail in Section II.

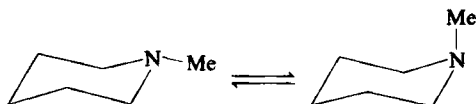
The results of kinetic protonation (Section II,H,1)^{125,168} and of nitrene addition¹⁷⁰ (Section II,H,2) give a high value (~ 2.7 kcal mol⁻¹) for the conformational free energy of the *N*-methyl group. This is supported by the ^{13}C -NMR line-broadening study¹⁰⁸ on 1,2,2,6-tetramethylpiperidine (detailed discussion in Section II,B,4), which gives ΔG° of 1.9 ± 0.2 kcal mol⁻¹ at -60°C , a lower value than for *N*-methylpiperidine as a result of flanking of the *N*-methyl group by two equatorial *C*-methyl groups.¹⁰⁹

One estimate of ΔG° based on ^{13}C -NMR shifts in *N*-methyldecahydroquinolines^{93,94} (detailed discussion in Section II,B,5) is lower than that based on different model systems,¹²⁵ and it made use of temperature dependence of ^{13}C -NMR shifts to give ΔG° 2.67–3.1 kcal mol⁻¹, in agreement with the protonation-based results.

The low values obtained from dipole-moment measurements^{119,124} and ultrasonic measurements¹⁷¹ together with the low value (ΔG° 1.4 kcal mol⁻¹) derived from a comparison¹¹³ of ^{15}N -NMR chemical shifts in systems such as 125 and 126 and in 127 and 128 with the small ^{15}N -NMR

¹⁷⁴ M. D. Rozeboom and K. N. Houk, *J. Am. Chem. Soc.* **104**, 1189 (1982).

TABLE XI
SUMMARY OF PUBLISHED WORK ON THE POSITION OF CONFORMATIONAL EQUILIBRIUM
IN *N*-METHYLPYPERIDINE

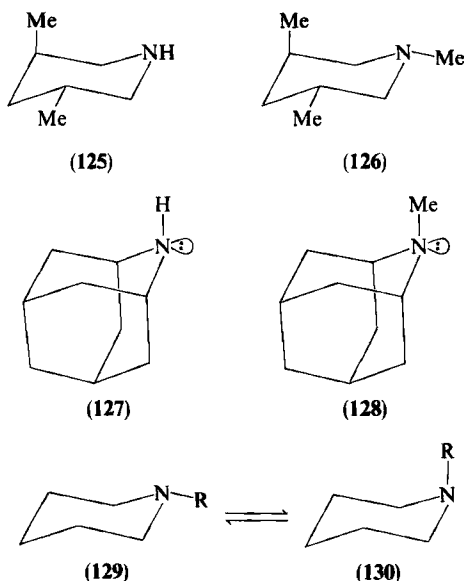


Phase	ΔG° (kcal mol ⁻¹) ^a	Method	Reference	Section of this review
Gas	0.78 (ΔH°)	Calculations	23	—
Various solvents	>0	¹ H-NMR chemical shifts	37, 42	II,B,1
CDCl ₃	>0	¹ H-NMR paramagnetic shifts	110	II,B,6
CCl ₄	>0	NMR chemical shifts	172	—
<i>n</i> -Dodecane	2.67–3.1	¹³ C-NMR shifts	125	This section
CDCl ₃	1.3–1.7 (31°C)	¹³ C-NMR shifts	93, 94	II,B,5
CF ₂ Cl ₂	1.9 ± 0.2 (–60°C)	¹³ C-NMR line broadening ^b	108	II,B,4
C ₆ H ₆	1.4 (37°C)	¹⁵ NMR shifts	113	This section
CCl ₄	1.6 (21°C)	IR	140	II,E,1
C ₆ H ₁₂	0.64	Dipole moments	119	II,D
Various	0.64–0.81	Dipole moments	124	II,D
None	1.6	Protonation	166	II,H,1
C ₆ H ₁₂	2.7 ± 0.2 (15°C)	Protonation	168	II,H,1
Gas	3.15 ± 0.1	} Protonation	125	II,H,1
<i>n</i> -Dodecane	3.0 ± 0.1			
C ₆ H ₆	2.5 ± 0.1			
CDCl ₃	2.4 ± 0.1			
C ₂ F ₃ Cl ₃	>2.6	Nitrene addition	170	II,H,2
None	0.88 (ΔH)	Ultrasonic measurements	171	II,I

^a A positive value refers to preference for *N*-Me equatorial.

^b These results refer to 1,2,2,6-tetramethylpiperidine which has a greater *N*-Me_{ax} preference than *N*-methylpiperidine.

shift changes observed on N-methylation of piperidine can no longer be considered reliable.



Thus the conformational free energy of the *N*-methyl group may be accepted as $2.7 \text{ kcal mol}^{-1}$ and the difference from that ($1.7 \text{ kcal mol}^{-1}$) in methylcyclohexane is primarily due to the changes in bond lengths, causing an increase in the syn-axial interactions in axial *N*-methylpiperidine.

NMR measurements⁹ give the barrier to ring inversion in *N*-methylpiperidine as $\Delta G^\ddagger_{-28^\circ}$ $11.8\text{--}12.0 \text{ kcal mol}^{-1}$. If a ΔG^\ddagger value of $6.0 \text{ kcal mol}^{-1}$ for the *N*-Me_{ax} \rightarrow transition state process, as suggested by ultrasonic measurements,¹⁷¹ is accepted (ΔG^\ddagger ultrasonic measurements are more reliable than ΔG° , see Section II,I) and if ΔG° for the *N*-methylpiperidine equilibrium is taken as $2.7 \text{ kcal mol}^{-1}$,¹²⁵ then the other half barrier (*N*-Me_{eq} \rightarrow transition state) is obtained² as $8.7 \text{ kcal mol}^{-1}$, which is consistent with the overall pattern of *N*-Me inversion half barriers.

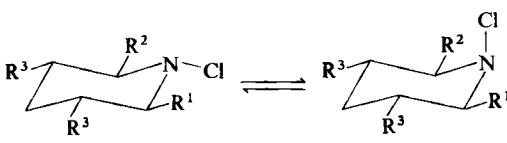
The values of ΔG^\ddagger (*N*-Me_{ax} \rightarrow transition state) of $9.1 \pm 0.3 \text{ kcal mol}^{-1}$ and ΔG^\ddagger (*N*-Me_{eq} \rightarrow transition state) of $11.0 \pm 0.3 \text{ kcal mol}^{-1}$ for 1,2,2,6-piperidine determined by a ¹³C-NMR line-broadening study¹⁰⁸ (detailed discussion in Section II,B,4) are higher than the corresponding values for *N*-methylpiperidine. These differences in barrier heights result from the interaction between the three vicinal methyl groups.

Dipole-moment measurements similar to those employed for 4-*p*-chlorophenyl-1-methylpiperidine were utilized to estimate ΔG° for the equilibrium $129 \rightleftharpoons 130$ (*R* = Et, *i*Pr), and these gave ΔG° for *N*-ethyl of $0.95 \text{ kcal mol}^{-1}$

(83.3% eq R) and ΔG° for *N*-isopropyl (92% eq R) of $1.44 \text{ kcal mol}^{-1}$ (cyclohexane solution at 25°C).¹²⁴ Although the trend is probably significant, it was however pointed out that considerable uncertainties existed in the quantitative significance of these results, and the more recent value^{93,94} of ΔG° $2.1 \text{ kcal mol}^{-1}$ for *N*-Et based on ^{13}C -NMR shifts (Section II,B,5) is more likely, although this may also be too low.^{174a}

c. *N*-Substituted Piperidines in Which the Substituent is Other than Alkyl. The ^{13}C -NMR spectrum of *N*-chloropiperidine at -98°C shows signals for both *N*-Cl_{ax} and *N*-Cl_{eq} conformers, permitting evaluation of ΔG° for the *N*-Cl_{eq} \rightleftharpoons *N*-Cl_{ax} equilibrium of $1.5 \pm 0.1 \text{ kcal mol}^{-1}$.¹⁷⁵ As in the case of *N*-methylpiperidine, this shows the increased equatorial preference of the *N*-substituent compared to the cyclohexane series (conformational free energy of chlorine in chlorocyclohexane $0.5 \text{ kcal mol}^{-1}$). The *N*-fluoro substituent also prefers the equatorial orientation.¹⁷⁶ Line-shape calculations give $\Delta G^\ddagger_{\text{ax} \rightarrow \text{eq}}$ $10.2 \pm 0.2 \text{ kcal mol}^{-1}$ and $\Delta G^\ddagger_{\text{eq} \rightarrow \text{ax}}$ $11.7 \pm 0.2 \text{ kcal mol}^{-1}$ for the *N*-chloropiperidine inversion.¹⁷⁵ Values of ΔG° for the conformational equilibria in *N*-chloropiperidine¹⁷⁵ and in methyl-substituted derivatives¹⁷⁷ are given in Table XII. These values show that a single 2-methyl substituent does not greatly change the position of conformational equilibrium from that in *N*-chloropiperidine, whereas when the *N*-chloro substituent is flanked by two equatorial methyl groups the equilibrium is markedly

TABLE XII
CONFORMATIONAL EQUILIBRIA IN *N*-CHLOROPIPERIDINES^{175,177}



<i>N</i> -Chloropiperidine			ΔG° (kcal mol ⁻¹)	Reference
R ¹	R ²	R ³		
H	H	H	1.5 ± 0.1 (-98°C)	175
H	H	Me	1.3 ± 0.2 (0°C)	177
Me	H	H	1.14 ± 0.03 (-50°C)	177
Me	Me	H	0.65 ± 0.02 (-50°C)	177

^{174a} Dr. M. J. T. Robinson has informed us that he and Dr. J. C. J. Barna have obtained $\Delta G^\circ = 2.9 \text{ kcal mol}^{-1}$ for *N*-ethylpiperidine at 293 K using 4-*tert*-butyl-1-ethylpiperidine and the method of Ref. 125.

¹⁷⁵ F. A. L. Anet and I. Yavari, *Tetrahedron Lett.*, 3207 (1977).

¹⁷⁶ J. Cantacuzene and J. Leroy, *J. Am. Chem. Soc.* **93**, 5263 (1971).

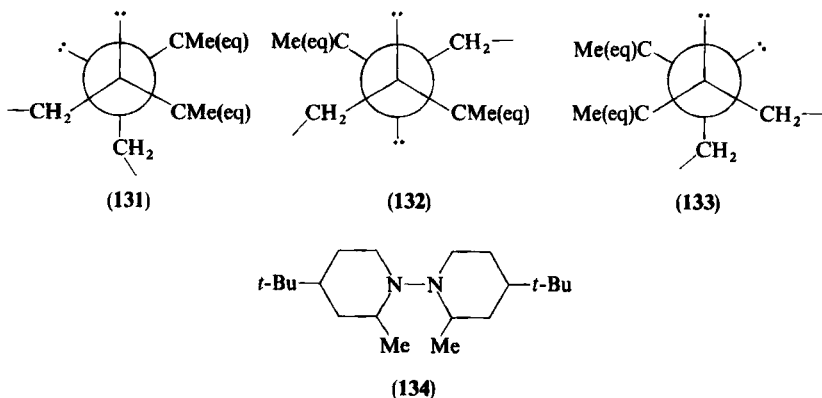
¹⁷⁷ K. W. Baldry and M. J. T. Robinson, *Tetrahedron* **31**, 2621 (1975).

shifted toward the N-axial chloro conformation.¹⁷⁷ This shift has been observed on going from *N*-methylpiperidine to 1,2,2,6-tetramethylpiperidine (Table XI) and in analogous 1,3-heterocyclic systems (Section III,D).

N-Nitroso-2,6-*cis*-dimethylpiperidine exists in the chair conformation with syn-axial methyl groups,¹⁷⁸ a situation reminiscent of that in 2-substituted cyclohexylenes.^{178a}

Chemical shifts indicate that *N*-methylsulfonyl groups in piperidines exist mainly in the equatorial orientation.¹⁷⁹ In *N*-alkylpiperidine *N*-oxides, the *N*-oxide group shows a strong preference for the axial position.¹⁸⁰ The planar or perpendicular orientation of the N—X=Y group in hindered piperidylamides and -amidines has been studied by ¹³C-NMR spectroscopy.^{180a}

The ΔG_c^\ddagger for the single-passing rotation about the N—N bond (**131** \rightleftharpoons **132** \rightleftharpoons **133**) in *meso*-1,1'-bis(*cis*-4-*tert*-butyl-2-methylpiperidine) (**134**) has been determined¹⁸¹ by a ¹³C-NMR study as 18.9 kcal mol⁻¹. A similar value is found for the same process in *meso*-1,1'-bis(2-methylpiperidine).¹⁸²



2. Conformational Equilibria of *C*-Substituents in Piperidine

The conformational free energies of *C*-methyl groups in piperidine and *N*-methylpiperidine have been estimated¹⁸³ by low temperature (−80 to

¹⁷⁸ R. R. Fraser and T. B. Grindley, *Can. J. Chem.* **53**, 2465 (1975).

^{178a} F. Johnson and D. T. Dix, *J. Amer. Chem. Soc.* **93**, 5931 (1971).

¹⁷⁹ A. R. Katritzky and M. Moreno-Manas, *An. Quim.* **71**, 804 (1975).

¹⁸⁰ M. J. Cook, A. R. Katritzky, and M. Moreno-Manas, *J. Chem. Soc. B*, 1330 (1971).

^{180a} L. Lunazzi, D. Macciantelli, D. Tassi, and A. Dondoni, *J. C. S. Perkin II*, 717 (1980).

¹⁸¹ K. Ogawa, Y. Takeuchi, H. Suzuki, and Y. Nomura, *J. C. S. Chem. Commun.*, 1015 (1981).

¹⁸² K. Ogawa, Y. Takeuchi, H. Suzuki, and Y. Nomura, *Chem. Lett.*, 697 (1981).

¹⁸³ E. L. Eliel, D. Kandasamy, and W. R. Kenan, Jr., *Tetrahedron Lett.*, 3765 (1976); E. L. Eliel, D. Kandasamy, C. Yen, and K. D. Hargrave, *J. Am. Chem. Soc.* **102**, 3698 (1980).

-95°C) ^{13}C -NMR spectroscopy. Figure 9 shows some representative examples with ^{13}C -NMR chemical shifts. The equilibrium constants were estimated from signal-area ratios, assuming no complications from unequal relaxation times. Assuming additivity of ΔG° values and taking the ΔG° value of $1.98\text{ kcal mol}^{-1}$ measured for the $4\text{-Me}_{\text{ax}} \rightleftharpoons 4\text{-Me}_{\text{eq}}$ -*N*-methylpiperidine equilibrium,¹⁶⁹ then the conformational free energies are as given in Table XIII.

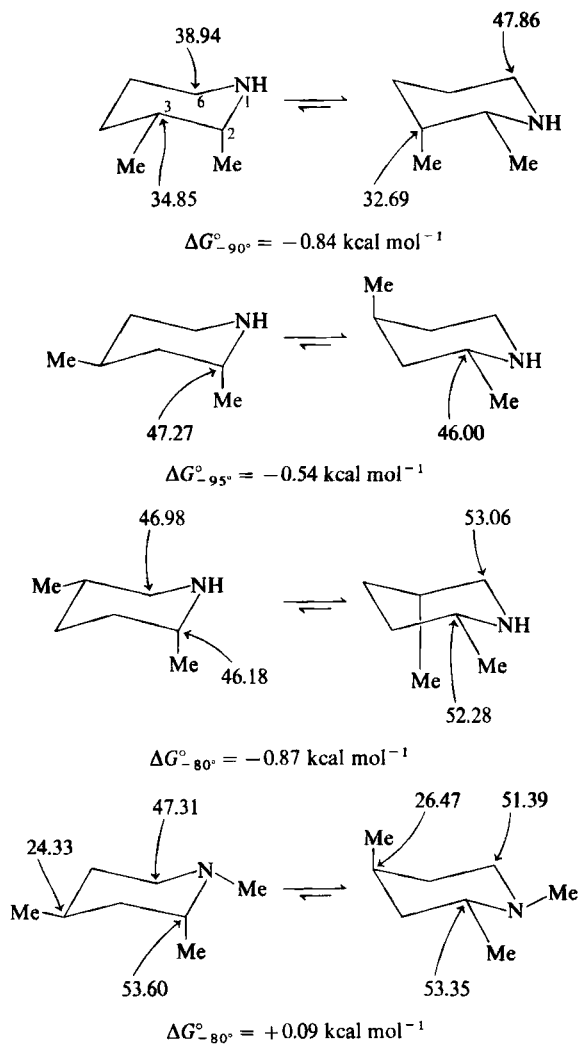


FIG. 9. Conformational equilibria and ^{13}C -NMR shifts in dimethylpiperidines.¹⁸³

TABLE XIII
CONFORMATIONAL FREE ENERGY OF METHYL GROUPS
IN PIPERIDINES^a

System	ΔG°	Reference
2-Me in piperidine	2.5 kcal mol ⁻¹	183
3-Me in piperidine	1.6 kcal mol ⁻¹	183
2-Me in <i>N</i> -methylpiperidine	1.9 kcal mol ⁻¹	183
3-Me in <i>N</i> -methylpiperidine	1.8 kcal mol ^{-1 b}	183
4-Me in <i>N</i> -methylpiperidine	1.98 \pm 0.07 kcal mol ⁻¹	169

^a Positive value indicates *N*-CH₃ equatorial is preferred.

^b Ref. 169 gives 1.51 \pm 0.07 kcal mol⁻¹.

The ΔG° value for 3-Me appears to be somewhat smaller than that for the 4-Me as expected for nonbonded interaction in the axial form with the nitrogen atom rather than with a CH bond. Most striking is the variation in conformational free energy of the 2-Me substituent in piperidine and its *N*-methyl derivative. The lower value in the *N*-methylpiperidine must be a result of an interaction between 2-Me_{eq} and *N*-Me, caused by puckering at the nitrogen end of the chair.

The preference for the axial position of 2-alkyl substituents is dramatically increased by the presence of *N*-nitro-,¹⁸⁴ *N*-acetyl-,^{185,186} *N*-benzoyl-,¹⁸⁷ and related substituents (cf. *N*-nitroso-2,6-*cis*-dimethylpiperidine,¹⁷⁸ Section III,A,1).

Intramolecular hydrogen-bonding studies provide information concerning conformation in hydroxypiperidines, especially in the case of 3-hydroxypiperidines^{187a} (see also Section II,E,3). Use of the protonation technique (Section II,J,1) has shown a conformational equilibrium for 1-alkyl-3-hydroxypiperidines with the axial OH conformer dominant (69% in apolar solvent).^{187b} The value of ΔG° for the *N*-methyl-4-piperidinol equilibrium has been estimated as 0.82 kcal mol⁻¹ (CDCl₃, 40°C, favoring OH equatorial) a value similar to that for cyclohexanol.¹⁸⁸ Studies of more heavily substituted 4-piperidinols indicate a significant population of the skew-boat conformation by *c*-2-Me,*t*-5-Me,*r*-4-OH-1,2,5-trimethyl-4-hydroxy-4-phenylpiperi-

¹⁸⁴ H. Ripperger, *Z. Chem.* **17**, 177 (1977).

¹⁸⁵ H. Paulsen, K. Todt, and H. Ripperger, *Chem. Ber.* **101**, 3365 (1968).

¹⁸⁶ R. R. Fraser and T. B. Grindley, *Tetrahedron Lett.*, 4169 (1974).

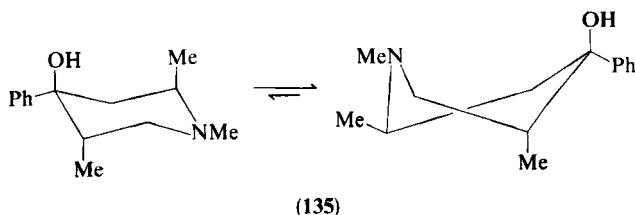
¹⁸⁷ R. A. Johnson, *J. Org. Chem.* **33**, 3627 (1968).

^{187a} H. S. Aaron and C. P. Ferguson, *Tetrahedron* **30**, 803 (1974); *J. Am. Chem. Soc.* **98**, 7013 (1976).

^{187b} J. J. Van Luppen, J. A. Lepoivre, R. A. Dommissie and F. C. Alderweireldt, *Org. Magn. Reson.* **18**, 199 (1982).

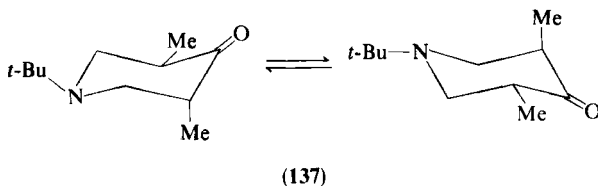
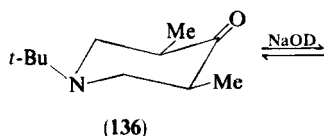
¹⁸⁸ C.-Y. Chen and R. J. W. Le Fèvre, *Tetrahedron Lett.*, 4057 (1965).

dine (135)¹⁸⁹ and of the boat conformation by the *c*-2-Me,*t*-3-Me,*r*-4-OH analog.^{189a} Semiquantitative estimations of the conformational free energies of the 4-chloro and 4-bromo substituents in *N*-methylpiperidines have been based on C-halogen IR absorption measurements.^{189b}



3. Conformational Equilibria in Piperidones

N-Methyl-4-piperidone¹⁹⁰ and *N*-methyl-3-piperidone¹⁹¹ both adopt the chair conformation. Examination^{192,193} of the 2- and 6-methylene proton signals in the NMR spectrum of the equilibrated (NaOD-D₂O) mixture of *cis*-dimethyl- (one conformer) (136) and *trans*-3,5-dimethyl-1-*tert*-butyl-4-piperidone (two conformers) (137) gave ΔG_{25}° values for the *cis* \rightleftharpoons *trans* equilibrium of 0.93 kcal mol⁻¹. This compares with a corresponding value of 1.415 kcal mol⁻¹ for the 2,6-dimethylcyclohexanone equilibrium. This increase in % axial methyl conformer in the heterocycle suggests that repulsive interactions between the methyl group and the nitrogen lone pair are less than that between the alkyl group and a CH group.¹⁹³



¹⁸⁹ A. F. Casy and K. M. J. McErlane, *J. C. S. Perkin I*, 334 (1972).

^{189a} A. F. Casy, F. O. Ogungbamila, and C. Rostron, *J. C. S. Perkin I*, 749 (1982).

^{189b} H. Remane, R. Borsdorf, G. Nord, and U. Pfestorf, *J. Prakt. Chem.* **322**, 638 (1980).

¹⁹⁰ N. L. Allinger and S. P. Jindal, *J. Org. Chem.* **37**, 1042 (1972).

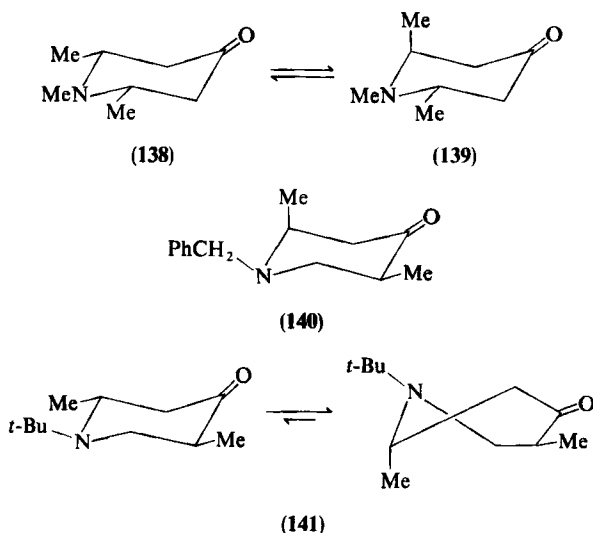
¹⁹¹ J. A. Hirsch and A. A. Jarmas, *J. Org. Chem.* **43**, 4106 (1978).

¹⁹² P. J. Brignell, A. R. Katritzky, and P. L. Russell, *Chem. Commun.*, 723 (1966).

¹⁹³ P. J. Brignell, A. R. Katritzky, and P. L. Russell, *J. Chem. Soc. B*, 1459 (1968).

Similar studies¹⁹⁴ on 1-*p*-methoxy-, *p*-methyl-, and *p*-chlorophenyl-3,5-dimethyl-4-piperidone show similar ΔG° values to that for the 1-*tert*-butyl analog and no significant variation with aryl substituents. This work suggests that the axial methyl group is insufficiently sensitive a probe to detect small changes in geometry about a piperidine-ring nitrogen caused by small changes in hybridization resulting from alteration of para substituents in an aryl group or even from the change of aryl to alkyl.

Epimerization studies on *cis*- \rightleftharpoons *trans*-1,2,6-trimethyl-4-piperidone (**138** \rightleftharpoons **139**) gave a low conformational free energy (0.47 kcal mol⁻¹ at 50°C) for the 2-methyl group,¹⁹⁵ presumably due to interaction between the methyl group and the N-substituent. The 2-methyl group is axial in the preferred conformation of 1-benzyl-*cis*-2,5-dimethyl-4-piperidone (**140**).¹⁹⁶



Heavily substituted piperidones, for example 1-*tert*-butyl-*trans*-2,5-dimethylpiperidone (**141**), may adopt skew-boat conformations.¹⁹⁷

4. Conformational Equilibria of 4-Spiropiperidines

The use of dipole moments and low-temperature NMR measurements on 4-spiro-1-*tert*-butylpiperidines and 5-spiro-1,3-dioxanes has been developed

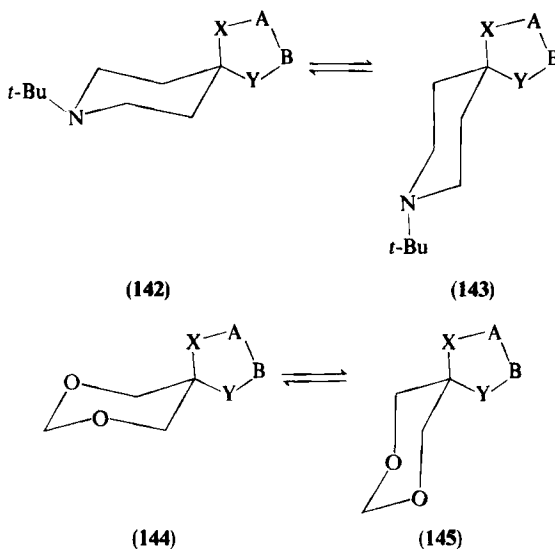
¹⁹⁴ M. D. Brown, M. J. Cook, G. Desimoni, and A. R. Katritzky, *Tetrahedron* **26**, 5281 (1970).

¹⁹⁵ E. A. Mistryukov and G. N. Smirnova, *Tetrahedron* **27**, 375 (1971).

¹⁹⁶ M. M. A. Hassan and A. F. Casy, *Org. Magn. Reson.* **2**, 197 (1970).

¹⁹⁷ M. M. A. Hassan and A. F. Casy, *Tetrahedron* **26**, 4517 (1970).

into a general method for investigating intramolecular interactions in situations of defined geometry.^{121,198-202} In compounds of type **142** \rightleftharpoons **143** and **144** \rightleftharpoons **145** (and similar derivatives with three or four-membered spiro rings), X and Y are held at a known orientation and distance to the probe of 1,3-diaxial interaction: a comparison between the two systems allows comparison of H atoms and O lone pairs as probes. In this series good agreement is obtained between the results of dipole moment and low-temperature NMR analysis.



The dipole moments of the two conformers **146** and **147** of 1-*tert*-butylpiperidine-4-spiro-4'(1',3'-dioxolan) were calculated by vector addition of the moments of 1-*tert*-butylpiperidine and 4,4-dimethyl-1,3-dioxolan, making reasonable assumptions regarding geometries. This gave 1.15 and 1.93 D as the moments of the two conformers. The observed moment of 1.47 D gave ΔG° of 0.37 kcal mol⁻¹ in favor of the axial oxygen conformer **146** in cyclohexane solution. ΔG_{62}° of 0.26 kcal mol⁻¹ was estimated from low-temperature ¹H-NMR studies.¹²¹ The differences between the piperidine and

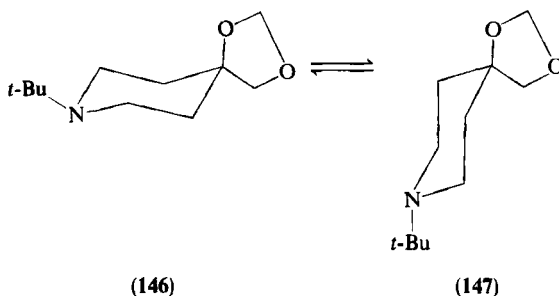
¹⁹⁸ R. A. Y. Jones, A. R. Katritzky, D. L. Nicol, and R. Scattergood, *J. C. S. Perkin II*, 337 (1973).

¹⁹⁹ R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, and B. B. Shapiro, *J. Chem. Soc. B*, 1308 (1971).

²⁰⁰ R. A. Y. Jones, A. R. Katritzky, and P. G. Lehman, *J. Chem. Soc. B*, 1316 (1971).

²⁰¹ R. A. Y. Jones, A. R. Katritzky, P. G. Lehman, A. C. Richards, and R. Scattergood, *J. C. S. Perkin II*, 41 (1972).

²⁰² R. A. Y. Jones, A. R. Katritzky, K. A. Record, R. Scattergood, and J. M. Sullivan, *J. C. S. Perkin II*, 402 (1974).



cyclohexane series shown in Table XIV¹⁹⁸ are probably due to dipole–dipole interactions.

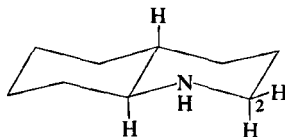
Dipole-moment measurements (in benzene) and low-temperature NMR studies (CDCl_3 – CFCl_3 or CDCl_3 – CCl_4 at -72 to -79°C) gave ΔG° values for other spiro systems. The ΔG° values shown in Table XIV are from the NMR measurements.^{199,200} Buttressing and inductive effects are probably responsible for variations in ΔG° values. The 1-*tert*-butylpiperidine-4-spiro-2'-oxiran and -2'-thiiran adopt equilibria favoring the axial heteroatom conformers (dipole-moment measurements) (Table XIV).²⁰¹

The preceding work shows clearly that the steric requirements of an oxygen atom are less than those of a CH_2 group where the probe is a CH at the β -axial position of a six-membered ring.

B. PIPERIDINES WITH FUSED RINGS

1. Decahydroquinolines

a. *trans*-Decahydroquinolines. First-order analysis of the 220 MHz NMR spectrum (CDCl_3 solution) of *trans*-decahydroquinoline is in accord with the twin-chair conformation **148** ($J_{2\text{ax},2\text{eq}} -11.7$; $J_{2\text{ax},3\text{ax}} 11.7$; $J_{2\text{ax},3\text{eq}} 3.2$ Hz).²⁰³ The stereochemical dependence of ^{15}N -NMR shifts in *trans*-decahydroquinolines has been described.^{203a}

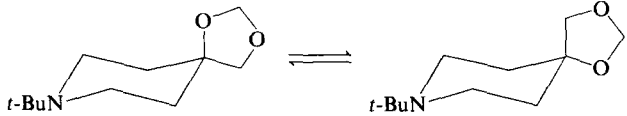
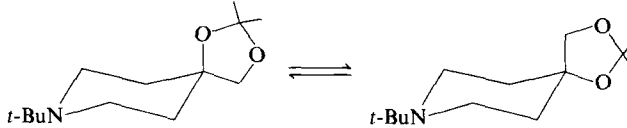
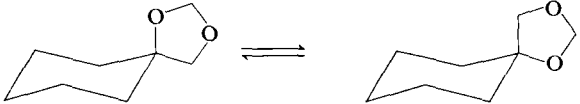
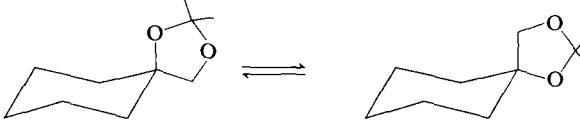
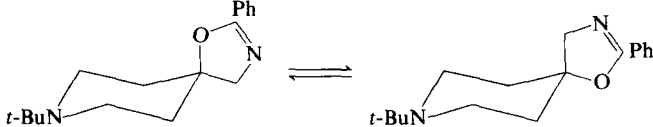


(148)

²⁰³ H. Booth and A. H. Bostock, *Chem. Commun.*, 177 (1967); *J. C. S. Perkin II*, 615 (1972).

^{203a} F. W. Vierhapper, G. T. Furst, R. L. Lichter, S. N. Y. Fanso-Free, and E. L. Eliel, *J. Am. Chem. Soc.* **103**, 5629 (1981).

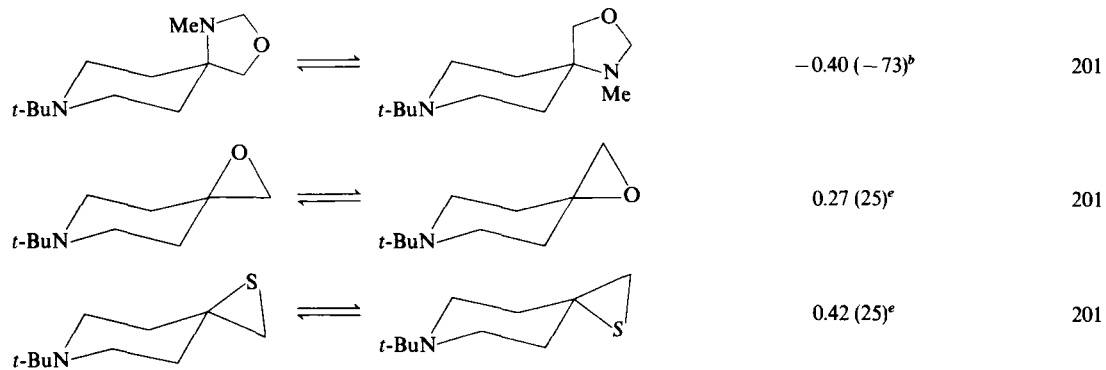
TABLE XIV
CONFORMATIONAL EQUILIBRIA IN SPIROPIPERIDINES

Structure	ΔG° (kcal mol ⁻¹) (°C)	Reference
	0.27 (−85) ^a	199
	0.21 (−80) ^a	199
	0.17 (−80) ^a	199
	0.05 (−80) ^a	199
	0.40 (−72) ^b	200

(continued)

TABLE XIV (continued)

Structure	ΔG° (kcal mol ⁻¹) (°C)	Reference
	0.60 (– 79) ^b	200
	– 0.17 (– 72) ^c	200
	0.28 (– 73) ^b	200
	0.12 (– 30) ^d	201
	– 0.09 (– 62) ^c	201



^a Solvent CFCl_3 .

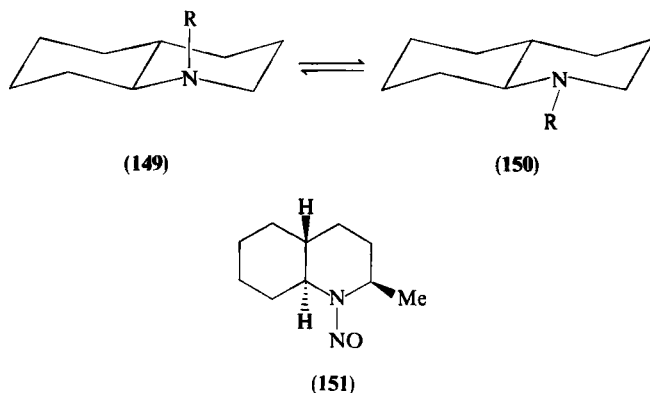
^b Solvent $\text{CDCl}_3\text{-CFCl}_3$.

^c Solvent $\text{CDCl}_3\text{-CCl}_4$.

^d Solvent CDCl_3 .

^e Solvent benzene.

The ΔG° values for the *N*-methyl- and *N*-ethyl-*trans*-decahydroquinoline equilibria **149** \rightleftharpoons **150** have been estimated⁹⁴ by ^{13}C -NMR spectroscopy (Section II,B,5) as -1.8 to -2.45 kcal mol $^{-1}$ for **149** ($\text{R} = \text{Me}$) \rightleftharpoons **150** ($\text{R} = \text{Me}$) and -2.1 kcal mol $^{-1}$ for **149** ($\text{R} = \text{Et}$) \rightleftharpoons **150** ($\text{R} = \text{Et}$).

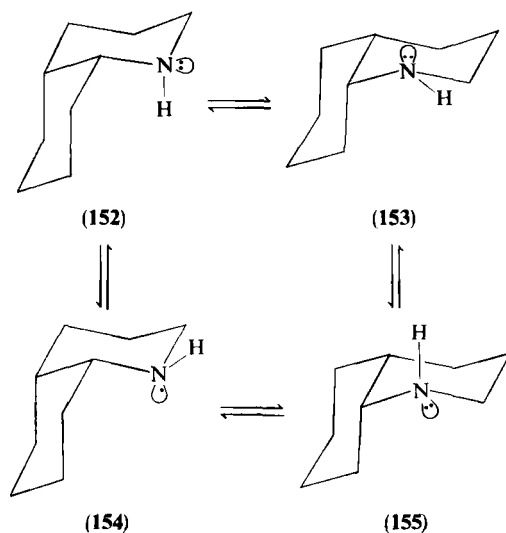


The conformational properties of a range of *N*-nitrosodecahydroquinolines have been based on ^{13}C - and ^1H -NMR spectral data. The *N*-nitroso-2 β -methyl-*trans*-decahydroquinoline (**151**), for example, in which the unfavorable interaction between substituents cannot be relieved by inversion as in *N*-nitroso-2,6-*cis*-dimethylpiperidine (Section III,C,1,c) adopts conformations with the piperidine ring in a boat or twist form.²⁰⁴

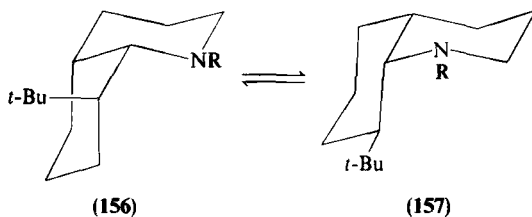
b. *cis*-Decahydroquinolines. *cis*-Decahydroquinoline may exist as an equilibrium between the four conformers **152**, **153**, **154**, and **155**, interconvertible by ring inversion and/or inversion at the nitrogen atom. The predominance of **152** or **154** in the equilibrium was demonstrated by the narrow width at half-height (8 Hz) of the angular 8 α -proton signals and the low-field absorption of the 7(ax)-proton syn-axial to the C—N bond.²⁰³ This preference for the N-inside *cis*-conformation was clearly shown by the ^{13}C -NMR spectrum at -74°C (CDCl_3), which showed signals for each conformer, giving 93.5% **152** \rightleftharpoons **154** and 6.5% **153** \rightleftharpoons **155**.²⁰⁵ (ΔG° 1.1 kcal mol $^{-1}$, favoring the N-inside conformers.) These values were obtained by a comparison of integrals for identically substituted carbon atoms in an attempt to avoid complications arising from differences in nuclear Overhauser enhancements and in spin-lattice relaxation times. 8 β -*tert*-Butyl-*cis*-decahydroquin-

²⁰⁴ F. W. Vierhapper, *J. Org. Chem.* **45**, 3111 (1980).

²⁰⁵ H. Booth and D. V. Griffiths, *J. C. S. Perkin II*, 842 (1973).



oline, like *cis*-decahydroquinoline, prefers (>97% **156**: R = H at -75°C) the N-inside *cis* conformation (**156**: R = H) with an axial *tert*-butyl group rather than the equatorially substituted alternative *cis* conformation (**157**: R = H), indicating a severe interaction between the nitrogen and *tert*-butyl group in conformation **157**: R = H.²⁰⁶ Equilibrium constants for methyl-substituted *cis*-decahydroquinolines have been derived from ^{15}N -NMR data.^{206a}



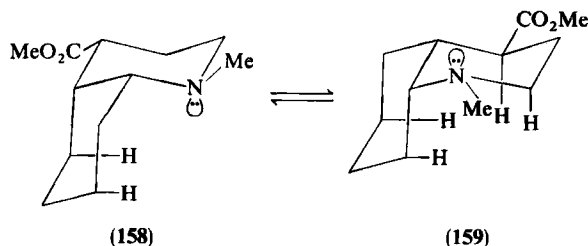
c. N-Substituted cis-Decahydroquinolines. Equilibration studies²⁰⁷ show that for the equilibrium **158** \rightleftharpoons **159** $\Delta G_{25^{\circ}}$ is $1.3 \text{ kcal mol}^{-1}$ in 1,2-dimethoxyethane and $\Delta G_{65^{\circ}}$ is $0.47 \text{ kcal mol}^{-1}$ in methanol. Thus **158** is

²⁰⁶ F. W. Vierhapper, *Tetrahedron Lett.* **22**, 5161 (1981).

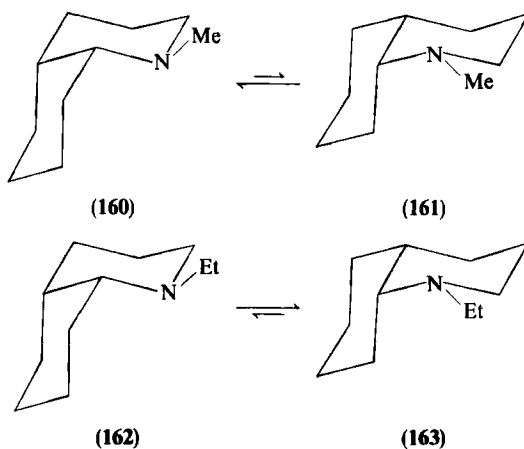
^{206a} F. W. Vierhapper, G. T. Furst, and R. L. Lichter, *Org. Magn. Reson.* **17**, 127 (1981).

²⁰⁷ K. Brown, A. R. Katritzky, and A. J. Waring, *Proc. Chem. Soc., London*, 257 (1964); *J. Chem. Soc. B*, 487 (1967).

avored in the nonhydrogen-bonding solvent because the interaction between the lone pair and C-7—H_{ax} in **158** is less than that between C-2—H_{ax} and C-8—H_{ax} in **159**. In methanol there is little conformational preference.



The 220 MHz NMR spectrum of *N*-methyl-*cis*-decahydroquinoline recorded at -30°C shows two *N*-Me singlets in the ratio 2:1 and the ^{13}C -NMR spectrum at -50°C enables the equilibrium to be estimated as 70% N-inside (**160**) \rightleftharpoons 30% N-outside (**161**). Replacement of *N*-Me by *N*-Et shifts the equilibrium **162** \rightleftharpoons **163** in favor of the N-outside conformation (86% **163**).⁸⁰



Because of the relatively short C—N bond length, the most unfavorable interaction in the N-outside^{207a} conformation involves C-2—N—C-8a—C-8, whereas the N-inside conformation is destabilized by the R—N—C-8a—C-8 interaction. This latter interaction increases with increasing size of

^{207a} For definition of "inside" and "outside" see structure **44a**.

the N-substituent R. On this basis the change in equilibria $160 \rightleftharpoons 161$ and $162 \rightleftharpoons 163$ may be rationalized.

On changing from 8 β -*tert*-butyl-*cis*-decahydroquinoline ($156 \rightleftharpoons 157$; R = H) to 8 β -*tert*-butyl-*N*-methyl-*cis*-decahydroquinoline ($156 \rightleftharpoons 157$; R = Me) the equilibrium shifts from >97% **156** (R = H) (at -75°C in CDCl_3) to 62% **156** (R = Me) and 38% **157** (R = Me) with an axial *N*-Me (at -80°C in CDCl_3). Explanations have been offered in terms of deformations caused by the *tert*-butyl group, altering the magnitudes of interactions from those in *N*-methylpiperidine.²⁰⁶

d. *Conformational Equilibria of C-Substituents in cis-Decahydroquinolines.* ^{13}C -NMR measurements have enabled the positions of equilibria of a variety of *C*-Me-substituted *cis*-decahydroquinolines to be estimated^{81,84} (Tables XV and XVI). The conformational free energy of the *C*-2-Me substituents may be estimated from the ΔG° values for the *cis*-decahydroquinoline equilibrium ($1.1 \text{ kcal mol}^{-1}$) and from entry 2 (Table XV) as greater than $2.7 \text{ kcal mol}^{-1}$, a value comparable with the *C*-2-Me in piperidine (Table XIII). Assuming the peri interaction between the methyl and *C*-5 methylene in the *N*-outside conformation of entry 4 (Table XV) to be equivalent to a *gauche*-butane interaction ($0.85 \text{ kcal mol}^{-1}$), then the conformational free energy of the *C*-4-Me substituent is $1.1 + 0.85 + 0.03 = 1.98 \text{ kcal mol}^{-1}$.⁸¹ In the case of entry 1 (Table XVI) the *C*-4a-Me contains two *gauche*-butane interactions in the *N*-inside conformer but one *gauche*-butane and one *gauche*-propylamine interaction in the alternative conformation, so that compared to the parent unsubstituted system a shift toward the *N*-outside conformation would have been expected. This is not observed, and it is suggested that in the *N*-outside conformation the unfavorable *C*-2—N—*C*-8a—*C*-8 interaction results in a bending apart of *C*-2 and *C*-8, forcing the *C*-3- H_{ax} and *C*-4-Me groups closer together, hence destabilizing this conformation.⁸⁴

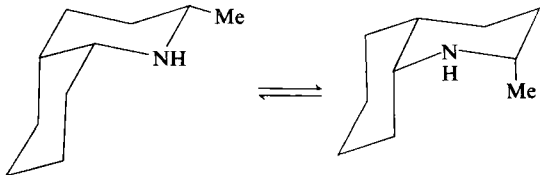
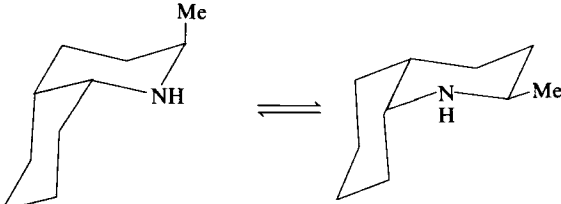
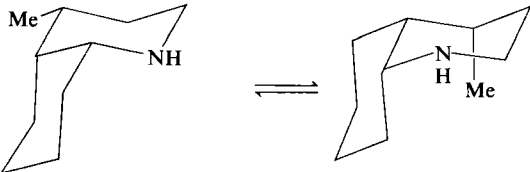
e. *Hydroxydecahydroquinolines and 2-Oxoctahydroquinolines.* The equatorial or axial orientation of the OH group in the 4-hydroxy-,²⁰⁸ the 5-hydroxy-,²⁰⁹ and the 7-hydroxy-*trans*-decahydroquinolines²¹⁰ have been assigned on the $W_{\frac{1}{2}}$ (peak widths at half-height) values of the CHOR signals in the spectra of the alcohols or derived tosylates. Whereas the *r*-4a,*c*-5,*c*-8a-5-hydroxy-*N*-methyldecahydroquinoline **164** prefers the *N*-inside

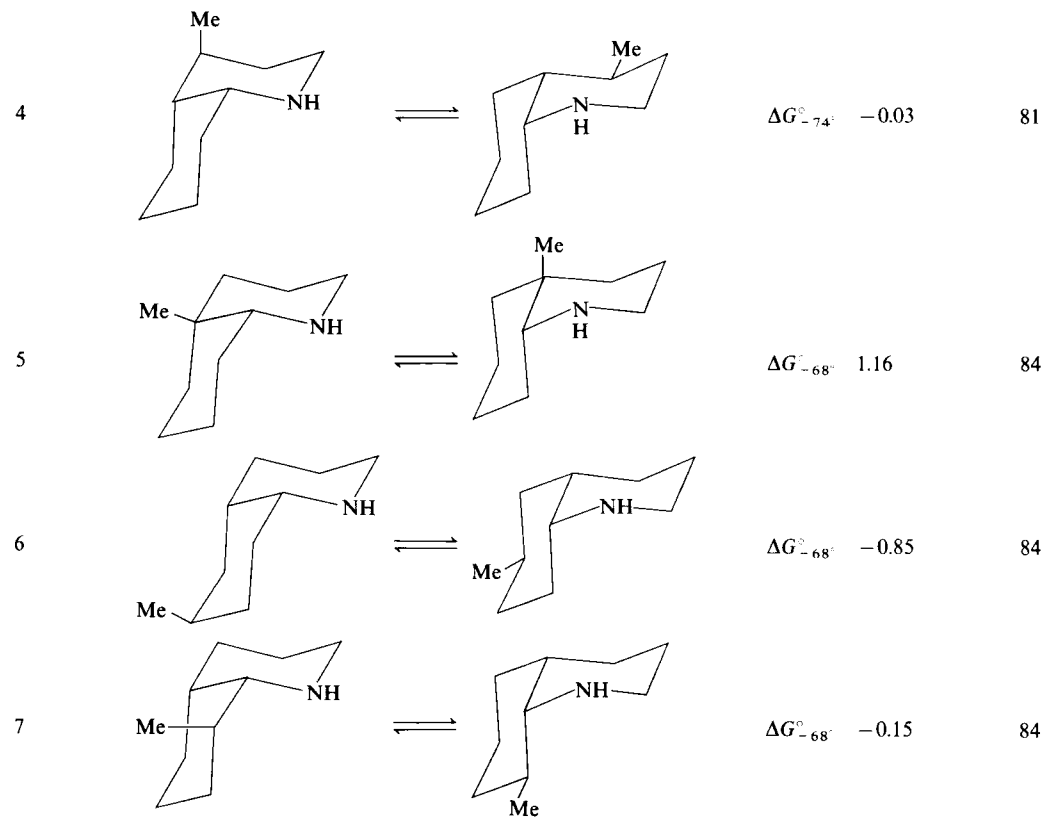
²⁰⁸ C. A. Grob and H. J. Lutz, *Helv. Chim. Acta* **48**, 791 (1965).

²⁰⁹ C. A. Grob and H. R. Kiefer, *Helv. Chim. Acta* **48**, 799 (1965).

²¹⁰ C. A. Grob and H. J. Wilkens, *Helv. Chim. Acta* **48**, 808 (1965).

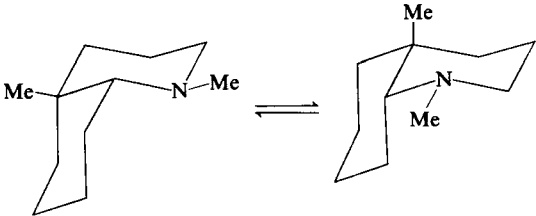
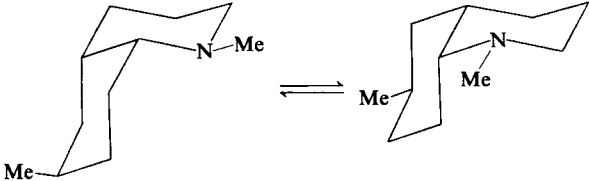
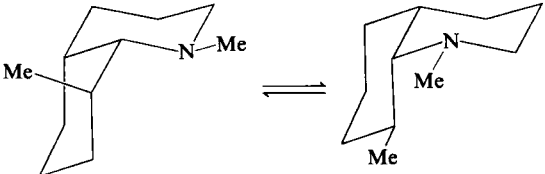
TABLE XV
CONFORMATIONAL EQUILIBRIA IN C-METHYL-*cis*-DECAHYDROQUINOLINES

Entry number		ΔG° (kcal mol ⁻¹) ^a	Reference
1		$\Delta G^\circ_{-74^\circ} > 1.6$	81
2		$\Delta G^\circ_{-74^\circ} < -1.6$	81
3		$\Delta G^\circ_{-74^\circ} > 2.0$	81



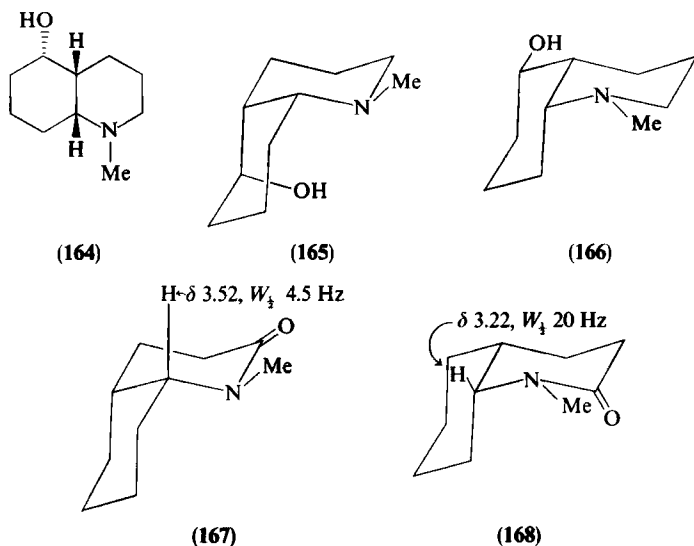
^a Positive value indicates predominance of first compound drawn.

TABLE XVI
CONFORMATIONAL EQUILIBRIA IN *C*-METHYL-*N*-METHYL-*cis*-DECAHYDROQUINOLINES⁸⁴

Entry number		$\Delta G_{-68^\circ}^\circ$ (kcal mol ⁻¹) ^a
1		0.49 ± 0.03
2		< -1.2
3		0.87 ± 0.07

^a Positive value indicates preference for first conformer drawn.

cis conformation **165** [as shown by IR evidence of intramolecular hydrogen bonding in **165** (3268 cm^{-1}) with only weak absorption (3597 cm^{-1}) from **166**], the corresponding acetate prefers the N-outside conformation.²¹⁰

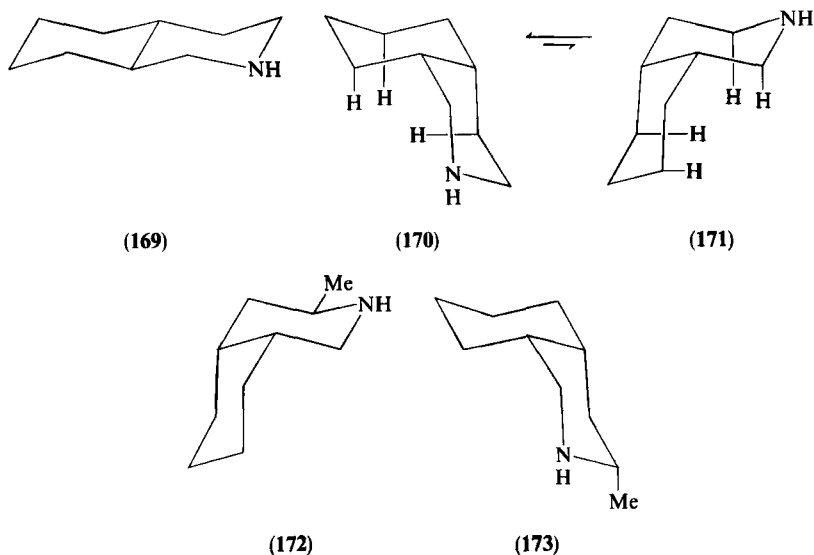


At -61°C the ^1H -NMR spectrum of *N*-methyl-*cis*-octahydrocarbostryl shows signals for 8a-H in both conformers **167** and **168**. On this basis $W_{\frac{1}{2}}$ values were recorded from room-temperature spectra of a variety of derivatives existing as equilibria. The *N*-inside conformation was preferred for the *N*-H compound, whereas the *N*-outside conformation was preferred for the *N*-Me compound. This is different from the situation in *N*-methyl-*cis*-decahydroquinoline and may be due to a closer approach of *N*-Me to the C-8 methylene in **167** than in **160** as a result of a flattened sp^2 -hybridized nitrogen atom.²¹¹

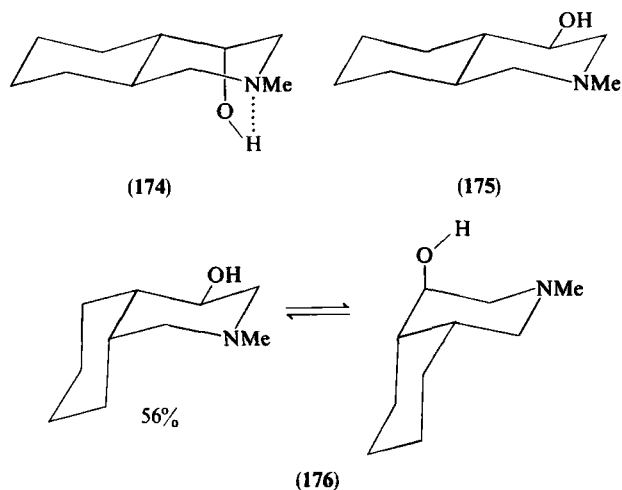
2. Decahydroisoquinolines

^1H - and ^{13}C -NMR spectra are consistent with the twin-chair conformation **169** for *trans*-decahydroisoquinoline, and ^{13}C -NMR spectroscopy gives $\Delta G_{-58^\circ}^\circ$ of $0.37\text{ kcal mol}^{-1}$ (70% *N*-inside conformation **170**) for the *cis*-decahydroisoquinoline equilibrium $\mathbf{170} \rightleftharpoons \mathbf{171}$,⁸² reflecting the difference between a *gauche*-butane and a *gauche*-propylamine interaction. The 3-methyl-*cis*-decahydroisoquinolines prefer the equatorial methyl conformations **172** and **173**.⁸²

²¹¹ T. Momose, T. Miyata, and T. Imanishi, *Heterocycles* **9**, 17 (1978).

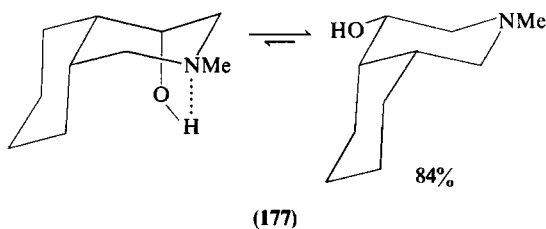


Configurations and preferred conformations of the monohydroxydecahydroisoquinolines may readily be assigned from a consideration of IR evidence of hydrogen bonding and of the W_z values of the CHOH protons. This is illustrated by the 4-hydroxydecahydroquinolines **174–177**.^{212,213}



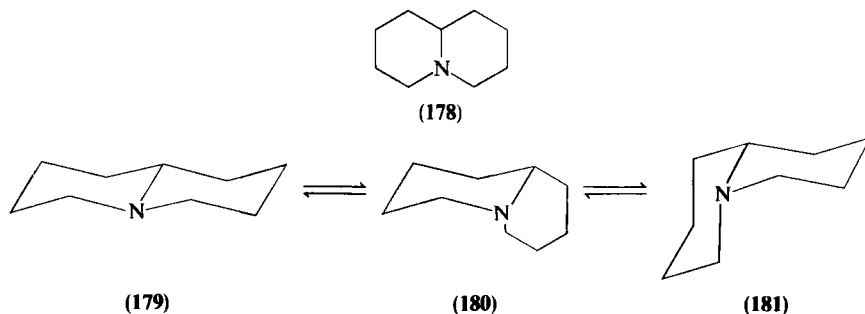
²¹² S. Kimoto, M. Okamoto, M. Uneo, S. Ohta, M. Nakamura, and T. Niiya, *Chem. Pharm. Bull.* **18**, 2141 (1970).

²¹³ S. Kimoto, M. Okamoto, A. Watanabe, T. Baba, and I. Dobashi, *Chem. Pharm. Bull.* **20**, 10 (1972).



3. Quinolizidines

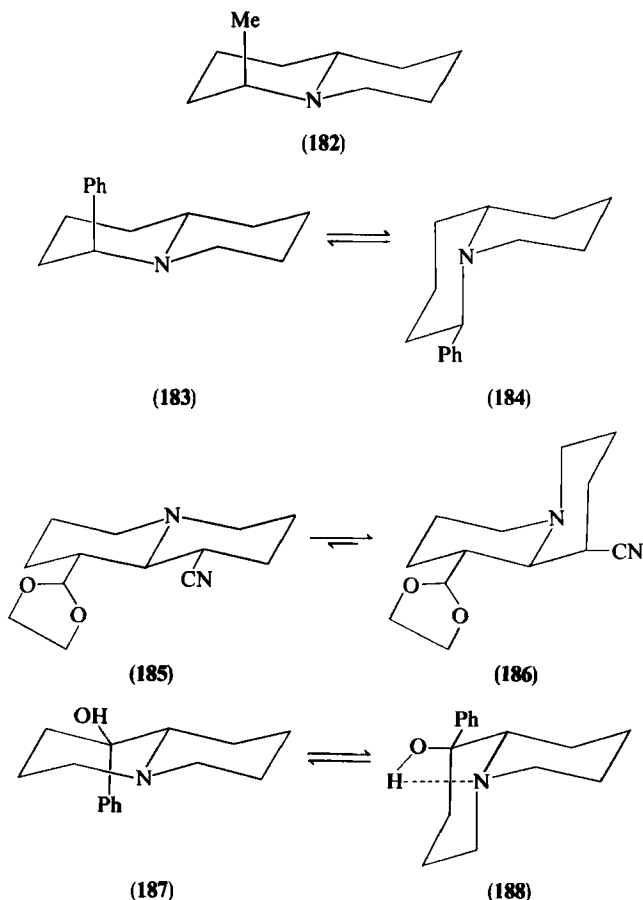
a. *Simple Quinolizidines.* Quinolizidine (178) may exist in solution as an equilibrium between the *trans*-fused conformer **179** and the *cis*-fused conformers **180** and **181**, interconvertible by ring reversal and/or nitrogen inversion. The large difference between the chemical shifts of the C-4 methylene protons (Section II,B,1) and the strong absorption in the 2800–2600 cm^{-1} region of the IR spectrum (Section II,E,1) indicate the predominance of the *trans* conformer **179**. The original estimation of ΔG_{25}° for the *cis* \rightleftharpoons *trans* equilibrium of $-4.4 \text{ kcal mol}^{-1}$ by a kinetic method has been described in detail (Section II,H,2) as has what is now considered to be the more reliable estimation ΔG° of $-2.6 \text{ kcal mol}^{-1}$ by H-bonding studies in the IR (Section II,E,3). This value compares with ΔG° of $-2.6 \text{ kcal mol}^{-1}$ for *cis*- and *trans*-decalin.



All the monomethyl- and monohydroxyquinolizidines exist predominantly in the *trans*-fused conformation and the early IR and ^1H -NMR studies on which these assignments were based (cf. especially Ref. 134) have been reviewed.¹⁴ The predominance of the *trans*-fused conformation for many quinolizidine derivatives has also been demonstrated by ^{13}C -NMR spectroscopy.^{79,86} The *trans*-fused conformation for **182**, the only *trans*-fused monomethylquinolizidine to show anomalous Bohlmann IR absorption (Section II,E,1), has been confirmed by ^{13}C -NMR spectroscopy.²¹⁴

²¹⁴ M. Sugiura and Y. Sasaki, *Chem. Pharm. Bull.* **24**, 2988 (1976).

Shifts toward the cis-fused conformation are shown by $183 \rightleftharpoons 184$, $185 \rightleftharpoons 186$, and $187 \rightleftharpoons 188$. Axial phenyl at C-4 in the trans conformation **183** shifts the equilibrium toward the cis conformation **184**³⁶ as does the unfavorable peri interaction in trans-fused **185**, which is relieved in the cis-fused conformation **186**.²¹⁵ The 1-hydroxyl-1-phenylquinolizidine **187** \rightleftharpoons **188** adopts an equilibrium containing 40% of the cis-fused conformation **188** in equilibrium with the trans-fused conformation **187**.¹⁴³

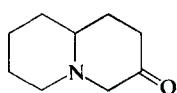


Quinolizidinones in general prefer trans-fused conformations but a comparison²¹⁶ of the value of J_{gem} for the C-4 methylene protons in quino-

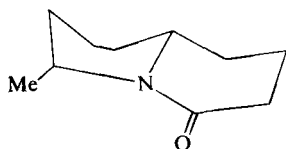
²¹⁵ E. Wenkert, B. Chauncy, K. G. Dave, A. R. Jeffcoat, F. M. Schell, and H. P. Schenk, *J. Am. Chem. Soc.* **95**, 8427 (1973).

²¹⁶ R. Cahill and T. A. Crabb, *Org. Magn. Reson.* **4**, 259 (1972).

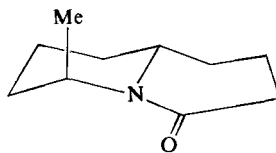
lizidine-3-one (**189**) with that calculated from the Barfield-Grant relationship⁶⁸ between J_{gem} in $\text{CH}_2\text{C}=\text{O}$ systems, and the π -bond/C—H dihedral angle suggests a trans-fused conformation in which the C=O bond is moved (relative to its situation in an unstrained Dreiding model) toward the angular C—H bond. Whereas the ^1H -NMR spectrum of *trans*-(6-*H*,9*a*-*H*)-6-methylquinolizidin-4-one is consistent with the chair piperidine ring shown in **191**,²¹⁸ the 6-proton shift in the spectrum of its 6-methyl epimer suggests distortion of the chair conformation as in **190**, presumably resulting from alleviation of an unfavorable Me/C=O interaction present in the undistorted chair conformation.²¹⁷



(189)



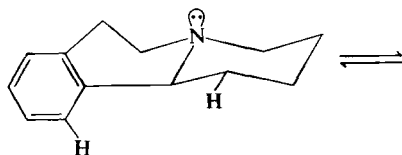
(190)



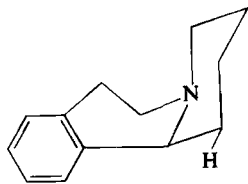
(191)

b. *Benzo*[*a*]quinolizidines (Including *Indolo*[2,3-*a*]quinolizidines). *Benzo*[*a*]quinolizidine may exist in solution as an equilibrium mixture of the trans-fused conformation **192** and two cis-fused conformations **193** and **194**. (Analogous conformations may be adopted by *indolo*[2,3-*a*]quinolizidine.)

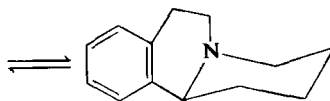
Investigations of the conformational equilibria by measurements of Bohlmann bands (Section II,E,1) and the chemical shift of the angular proton



(192)



(193)

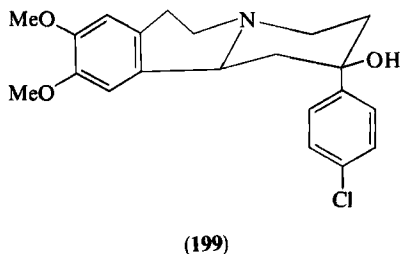
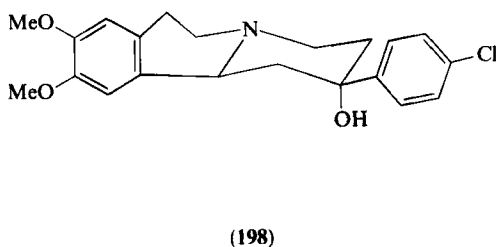
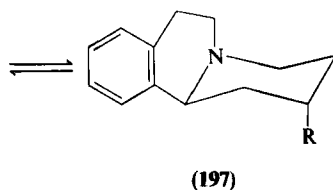
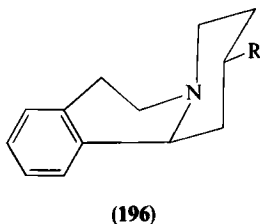
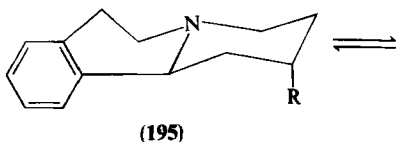


(194)

²¹⁷ R. Cahill and T. A. Crabb, *Org. Magn. Reson.* **5**, 295 (1973).

²¹⁸ F. Bohlmann and D. Schumann, *Tetrahedron Lett.*, 2435 (1965).

(11*b*-H or 12*b*-H) (Section II,B,1) have shown the predominance of the trans-fused conformation **192** for the unsubstituted compound^{48,219} and ¹³C-NMR chemical-shift measurements indicate ~92% of the trans-fused conformation **192** to be present.²²⁰



Substitution of **192** at C-2 by an axial substituent R pushes the equilibria $195 \rightleftharpoons 196 \rightleftharpoons 197$ toward the cis-fused conformation with an increasing percentage of the cis conformer with the increase in conformational free energy of the substituent R. Thus the 2-methyl isomer exists as a mixture of **195** (R = Me) and **196** (R = Me) in which **195** (R = Me) is favored,²²¹ the 2-aryl isomers favor the cis conformer **196** (R = aryl),⁴⁹ and the 2-*tert*-butyl compound **196** (R = *t*-Bu) exists exclusively as the cis conformer.²¹⁹

These results show ΔG° (trans \rightleftharpoons cis) for the benzo[*a*]quinolizidine to be less than that (2.6 kcal mol⁻¹) for the quinolizidine equilibrium.

Both the trans conformation **192** and one of the cis conformations **193** are destabilized by a nonbonded interaction between C-1-H and C-(11)-H, whereas **192** and **194** are possibly destabilized by an interaction between the nitrogen lone pair and the π -electron system of the benzene ring. [A

²¹⁹ G. W. Gribble and R. B. Nelson, *J. Org. Chem.* **38**, 2831 (1973).

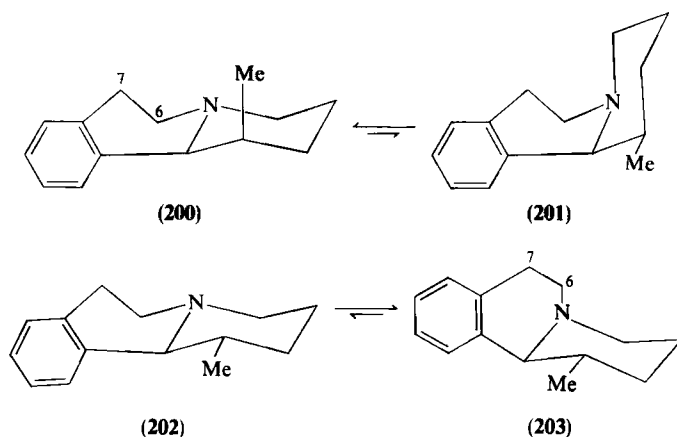
²²⁰ M. Sugiura, N. Takao, K. Iwasa, and Y. Sasaki, *Chem. Pharm. Bull.* **26**, 1901 (1978).

²²¹ J. Gootjes, A. M. de Roos, and W. T. Nauta, *Rec. Trav. Chim., Pays-Bas* **84**, 1183 (1965).

similar interaction has been invoked to explain the conformational equilibria in dihydro-1,2-oxazines (Section III,C).] The *cis* conformation **193** does not possess the unfavorable parallel lone pair- π -orbital geometry. The *cis* conformer **194** is destabilized by two *gauche*-butane interactions between the C-6 methylene and the C-1 and C-3 methylene groups, whereas the *cis* conformer **193** is destabilized by interactions between the fused benzene ring and the C-2 and C-4 methylenes and by a near *syn*-axial interaction between the C-4 and C-7 methylenes. The interactions involving the phenyl group may not, however, be as great as in axial phenylcyclohexane ($2.9 \text{ kcal mol}^{-1}$)^{221a} because in **193** the phenyl ring is held in one conformation, and placement of an axial methyl group in **192**, as in **195**, would not shift the equilibrium toward **196**, as observed if the nonbonded interactions involving the phenyl group were as high as $3.1 \text{ kcal mol}^{-1}$.³

The 2-hydroxy-2-(*p*-chlorophenyl)-9,10-dimethoxybenzo[*a*]quinolizidines both prefer the *trans*-fused conformations **198** and **199**²²² because the favored *cis* conformation **193** will carry an axial substituent at C-2, which undergoes considerable destabilization as a result of interaction with the phenyl group.

Comparison of $J_{13\text{C-H}}$ values (Section II,B,5) for the angular C-(11*b*)-H moiety in **192** ($J 125 \pm 2 \text{ Hz}$), in **200** \rightleftharpoons **201** ($J 122 \pm 3 \text{ Hz}$), and in **202** \rightleftharpoons **203** ($J 132 \pm 2 \text{ Hz}$) suggests the almost exclusive existence of the *cis*(1-H,11*b*-H) isomer as **200** and the *trans*(1-H,11*b*-H) isomer predominantly as the *cis*-fused conformation **203**. Conformations **201** and **202** are both destabilized by Me—C-11-H interactions.²²³



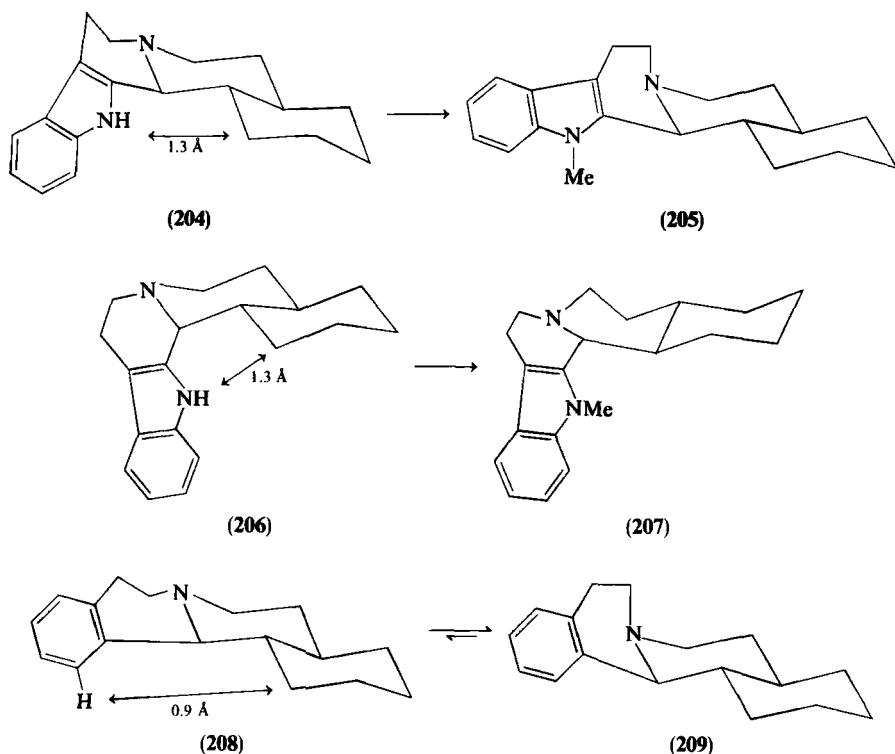
^{221a} E. L. Eliel and M. Manoharan, *J. Org. Chem.* **46**, 1959 (1981).

²²² H. Bruderer, M. Baumann, M. Uskoković, and A. Brossi, *Helv. Chim. Acta* **47**, 1852 (1964).

²²³ M. Sugiura, N. Takao, K. Iwasa, and Y. Sasaki, *Chem. Pharm. Bull.* **26**, 1168 (1978).

The two types of *cis* conformations **201** and **203** may be distinguished by the ^{13}C -NMR chemical shifts of the C-6 and C-7 nuclei (γ_{ax} -effect on C-7 in **201** and γ_{ax} -effect on C-6 in **203**), and consideration of such shifts for the 1-methylbenzo[*a*]quinolizidines along with Bohlmann-band measurements indicates²²⁰ 76% *cis*-fused conformation **203** for the *trans*(1-*H*,11*b-H*)-1-methyl isomer.

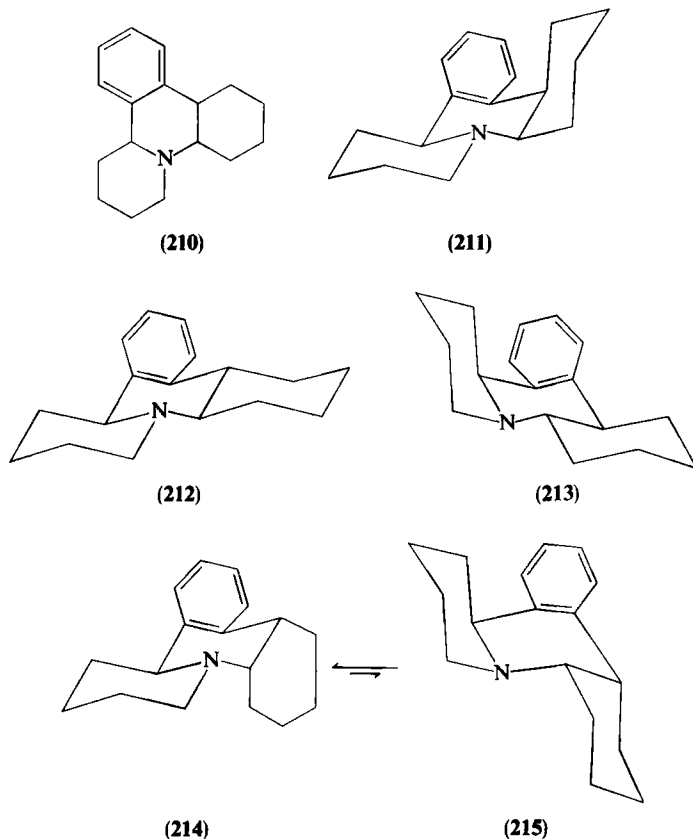
The "inside" yohimbanes also illustrate the importance of interring interactions, and marked changes in conformational equilibria are observed on N-methylation.⁵⁰ This is illustrated by the changes **204** \rightarrow **205** and **206** \rightarrow **207**. The benzo analog of **204** prefers the *cis* conformer **208** because the interring interaction is greater in *trans*-fused **209** than in **204**.²²⁴



Three isomers of the benzo[*a*]quinolizidine **210** adopt the *trans*-quinolizidine conformations **211**, **212**, and **213**, as shown by the J_{gem} values (Section II,B,2), Δ_{ac} values of the C-6 methylene protons, and the chemical shift of the angular proton (Section II,B,1). Both Δ_{ac} and the chemical shift of the

²²⁴ G. C. Morrison, W. A. Cetenko, and J. Shavel, Jr., *J. Org. Chem.* **36**, 3624 (1971).

angular proton are affected by the C-4 methylene in **214**, but the J_{gem} value of -12 Hz and reduced Bohlmann bands (Section II,E,1) suggest an equilibrium containing some of the *cis*-quinolizidine **215**.²²⁵

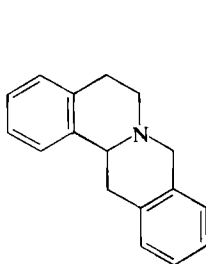


c. *Dibenzoquinolizidines*. The positions of conformational equilibria in the dibenzo[*a,g*]quinolizidines (**216**) are sensitive to the substitution in the aromatic ring, as shown by the differing conformational preferences of tetrahydropalmatine (**24**) and *O*-methylcapaurine (**25**),⁴⁸ discussed in Section II,B,1. The J_{gem} criterion (C-8 methylene protons) must be used with care because this parameter is sensitive to ring-D substitution (Section II,B,2). The monomethyldibenzo[*a,g*]quinolizidines **217**, **218**,⁴⁸ **219**, and **220**.²²⁶

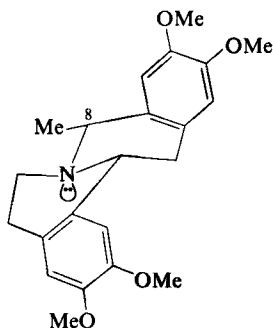
²²⁵ G. Van Binst and G. Laus, *Org. Magn. Reson.* **9**, 467 (1977).

²²⁶ D. W. Hughes, H. L. Holland, and D. B. MacLean, *Can. J. Chem.* **54**, 2252 (1976).

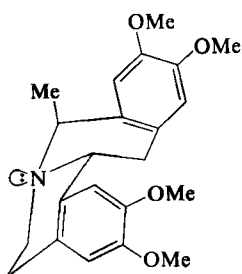
adopt the conformations shown, indicating the smaller conformational free-energy difference between cis and trans conformers in this series than in quinolizidine itself (see discussion in Section III,B,3,b).



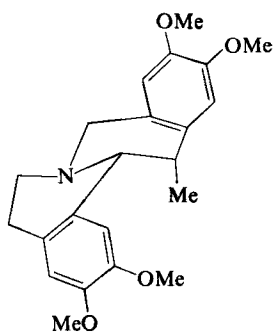
(216)



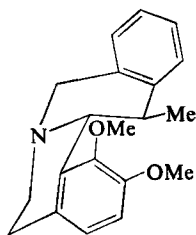
(217)



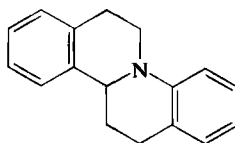
(218)



(219)



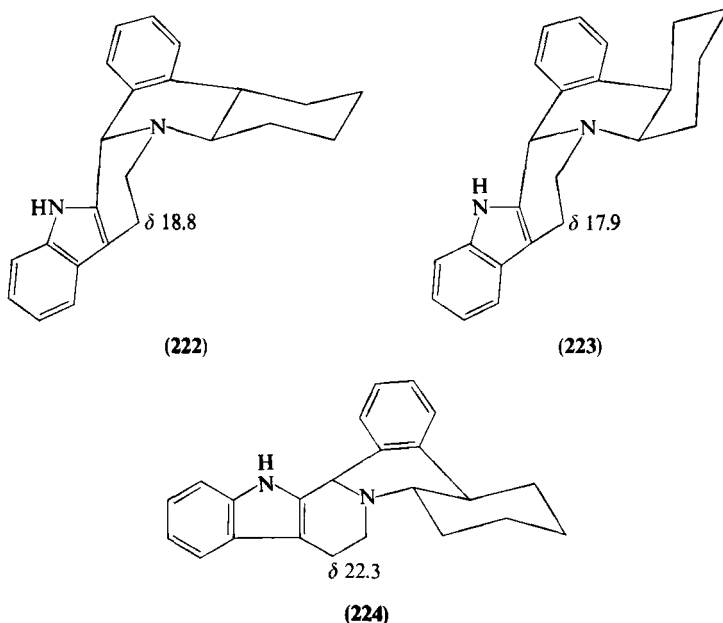
(220)



(221)

Similar aromatic ring-substitution effects on conformational equilibria to those shown by **216** are shown by the dibenzo[*a,f*]quinolizidines (**221**). Examples are provided by **29** and **30**,⁵¹ described in Section II,B,1. In these systems J_{gem} and angular proton shifts are sensitive to aromatic ring-orbital–nitrogen lone-pair overlap (Sections II,B,1 and 2).

The more complicated $[a,h]$ systems **222**–**224** prefer the cis-fused conformations, and the two different types **222** and **223**, compared to **224**, may be distinguished by the ^{13}C -NMR shifts of the indole benzylic methylene²²⁷ (Section II,B,5).



4. Tropanes and 3-Azabicyclo[3.3.1]nonanes

Early work had suggested that unquaternized tropanes **225** \rightleftharpoons **226** exist mainly in the N-substituent axial form **226** (for a review, see Ref. 228). However, ^1H -NMR and dipole-moment studies showed that the N-equatorial conformation for **225** predominated.²²⁹ Kinetically controlled protonation²³⁰ and the line broadening technique²³¹ indicate that there is $\sim 87\%$ of the N-equatorial conformation **225** present in the equilibrium

²²⁷ G. Van Binst, D. Tourwé, and E. De Cock, *Org. Magn. Reson.* **8**, 618 (1976).

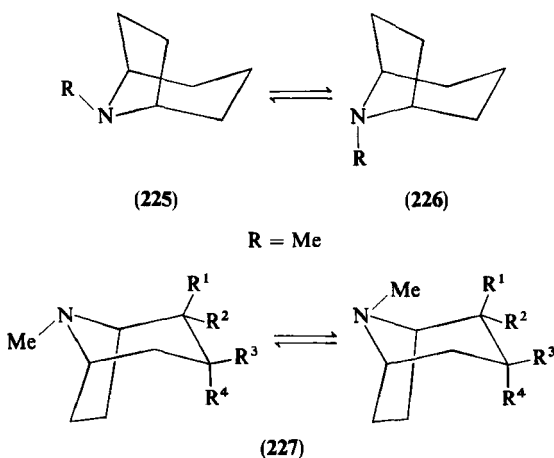
²²⁸ G. Fodor, *Tetrahedron* **1**, 86 (1957).

²²⁹ R. J. Bishop, G. Fodor, A. R. Katritzky, F. Soti, L. E. Sutton, and F. J. Swinbourne, *J. Chem. Soc. C*, 74 (1966).

²³⁰ D. C. Appleton, J. McKenna, J. M. McKenna, L. B. Sims, and A. R. Walley, *J. Am. Chem. Soc.* **98**, 292 (1976).

²³¹ V. J. Baker, J. Ferguson, A. R. Katritzky, and R. C. Patel, *Tetrahedron Lett.*, 4735 (1976).

225 \rightleftharpoons **226**, ($R = \text{Me}$). The ^{13}C -NMR shifts for the $N\text{-Me}_{\text{ax}}$ and $N\text{-Me}_{\text{eq}}$ conformers of tropine (**227**: $R^1 = R^3 = R^4 = \text{H}$, $R^2 = \text{OH}$) and of pseudotropine (**227**: $R^1 = \text{OH}$, $R^2 = R^3 = R^4 = \text{H}$) have been obtained from spectra recorded at -70°C . Comparison of these parameters with those for cocaine ($R^1 = \text{CO}_2\text{Me}$, $R^2 = R^4 = \text{H}$, $R^3 = \text{OCOPh}$) and its isomers suggests that, for example, pseudococaine (**227**: $R^1 = R^4 = \text{H}$, $R^2 = \text{CO}_2\text{Me}$, $R^3 = \text{OCOPh}$) has a larger percentage of $N\text{-Me}_{\text{ax}}$ conformer in its equilibrium than has cocaine.²³² ΔG_{25}° 1.3 kcal mol $^{-1}$ has been deduced for the tropinone N -oxide (axial N -oxide–equatorial N -oxide) equilibration showing the larger steric requirement of the methyl group than the oxygen atom.^{232a} ^1H -NMR spectral studies show that, whereas a 3α -anilinetropine (**227**: $R^1 = R^2 = R^3 = \text{H}$, $R^4 = \text{NHPh}$) adopts a flattened piperidine ring conformation, 3α -propananilidotropine [**227**: $R^1 = R^2 = R^3 = \text{H}$, $R^4 = \text{N(Ph)-CO}_2\text{Et}$] adopts a boat piperidine ring.²³³ The conformation of atropine and scopolamine cations have been determined by the differential NMR shielding effects from the aromatic substituent,^{233a} and related work has been reported on cocaine isomers.^{233b}



The stereochemistry of 3-azabicyclo[3.3.1]nonanes has been extensively reviewed.²³⁴

²³² H. J. Schneider and L. Sturm, *Angew. Chem., Int. Ed. Engl.* **15**, 545 (1976).

^{232a} Y. Shvo and E. D. Kaufman, *J. Org. Chem.* **47**, 2190 (1982).

²³³ J. R. Bagley and T. N. Riley, *J. Heterocycl. Chem.* **14**, 599 (1977).

^{233a} J. Feeney, R. Foster, and E. A. Piper, *J. C. S. Perkin II*, 2016 (1977).

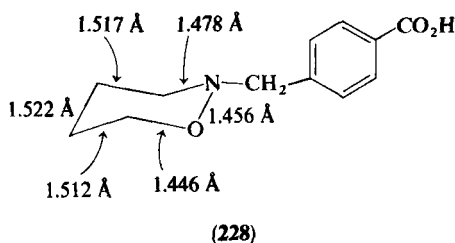
^{233b} F. I. Carroll, M. L. Coleman, and A. H. Lewin, *J. Org. Chem.* **47**, 13 (1982).

²³⁴ R. Jeyaraman and S. Avila, *Chem. Rev.* **81**, 149 (1981).

C. 1,2-HETEROCYCLIC SYSTEMS

1. Tetrahydro-1,2-oxazines and Dihydro-1,2-oxazines

An X-ray study²³⁵ of *N*-(*p*-carboxybenzyl)tetrahydro-1,2-oxazine shows the ring to be more puckered than in cyclohexane (see torsion angles with structure **228**). The IR spectrum of tetrahydro-1,2-oxazine itself shows a single band in the *N*-H overtone region (Section II,E,2) at 6497 cm^{-1} , assigned to *N*-H equatorial.^{236,237} The equatorial preference of the *N*-substituent in **228** is maintained for *N*-alkyl groups in tetrahydro-1,2-oxazines: the photoelectron spectra (Section II,F) of *N*-methyl and *N*-*tert*-butyl derivatives each showing only the two bands corresponding to the equatorial conformers.²³⁸ The *N*-Me_{eq} preference is supported by dipole-moment measurements (Section II,D) on 6-aryl-2-methyltetrahydro-1,2-oxazine, which gives an approximate ΔG_{25}° of 1.9 kcal mol^{-1} favoring the *N*-Me_{eq} conformer²³⁷; however, this should be taken as a minimum value, and work on tetrahydro-1,4,2-dioxazines (Section III,F,1) suggests a higher value of 3.7 kcal mol^{-1} .



Torsion angles	
O—N—C-3—C-4	64.3°
N—C-3—C-4—C-5	57.9°
C-3—C-4—C-5—C-6	53.1°
C-4—C-5—C-6—O	56.2°
C-5—C-6—O—N	63.2°
C-6—O—N—C-3	67.1°

The low temperature $^1\text{H-NMR}$ spectrum (CD_2Cl_2 , -40°C) of 2,5-dimethyltetrahydro-1,2-oxazine (equilibrium shown in Fig. 10) shows an equilibrium between **229** (95%) and **232** (5%).²³⁹ The *N*-Me_{ax} conformers **230** and **231** are neglected because even tetrahydro-1,2-oxazine itself exists exclusively as the *N*-H_{eq} conformer,²³⁷ and calculations on hydroxylamine indicate a very high energy for conformations that correspond to axial *N*-substituents.²⁴⁰ Thus the conformational free energy of the 5-methyl group may be estimated as $1.36 \pm 0.1\text{ kcal mol}^{-1}$ at -40°C .²³⁹

²³⁵ F. G. Riddell, P. Murray-Rust, and J. Murray-Rust, *Tetrahedron* **30**, 1087 (1974).

²³⁶ R. A. Y. Jones, A. R. Katritzky, A. C. Richards, S. Saba, A. J. Sparrow, and D. L. Trepanier, *Chem. Commun.*, 673 (1972).

²³⁷ R. A. Y. Jones, A. R. Katritzky, S. Saba, and A. J. Sparrow, *J. C. S. Perkin II*, 1554 (1974).

²³⁸ P. Rademacher and B. Freckmann, *Tetrahedron Lett.*, 841 (1978).

²³⁹ F. G. Riddell, *Tetrahedron* **31**, 523 (1975).

²⁴⁰ W. H. Fink, D. C. Pan, and L. C. Allen, *J. Chem. Phys.* **47**, 895 (1967).

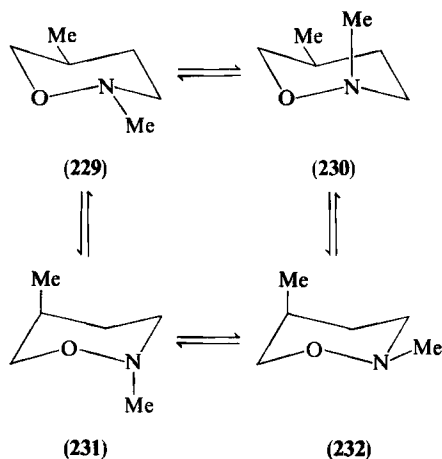
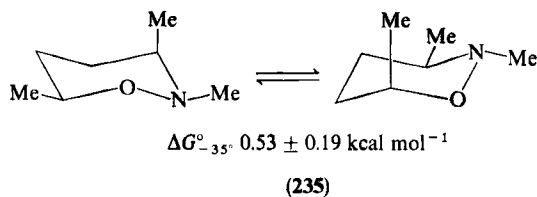
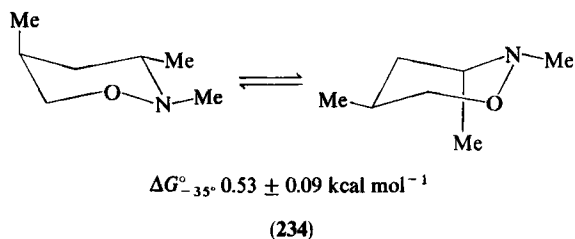
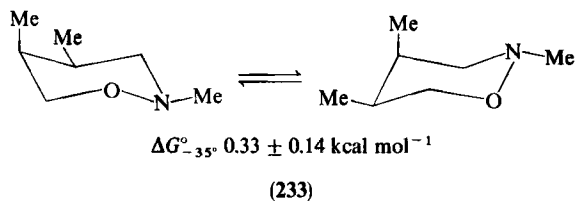


FIG. 10. Conformational equilibrium for 2,5-dimethyltetrahydro-1,2-oxazine.

Analysis of the ^1H -NMR spectra of the trimethyltetrahydro-1,2-oxazines **233**, **234**, and **235** at -35°C when nitrogen inversion is considered to be slow (see below) permits the conformational free energies of methyl substituents (Table XVII) to be estimated²⁴¹ if the $\Delta G_{5-\text{Me}}^\circ$ value derived above is used.

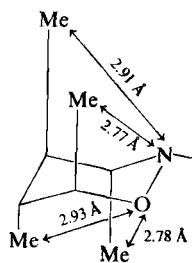


²⁴¹ F. G. Riddell and D. A. R. Williams, *Tetrahedron* **30**, 1097 (1974).

TABLE XVII
ESTIMATED CONFORMATIONAL Free ENERGIES OF
METHYL SUBSTITUENTS IN
TETRAHYDRO-1,2-OXAZINES^{239,241}

Substituent	Estimated ΔG° (kcal mol ⁻¹ , CH ₂ Cl ₂ , at -35°C)
3-Me	1.89 \pm 0.2
4-Me	1.70 \pm 0.25
5-Me	1.36 \pm 0.1
6-Me	2.42 \pm 0.4

If these results are compared with calculated transannular distances shown in **236** for axial methyl groups based on X-ray data,²³⁵ then not only are the effects of bond-length changes on ΔG° evident (cf. 4-Me and 6-Me) but also interactions between axial methyl and oxygen is seen to be less than that between axial methyl and nitrogen.²⁴¹



(236)

The low-temperature ¹H-NMR spectrum of *N*-methyltetrahydro-1,2-oxazine shows nonequivalence of the *N*-CH₂ protons, giving ΔG^\ddagger of 13.7 \pm 0.5 kcal mol⁻¹ (coalescence temperature +5 \pm 5°C) for the process observed. Because the coalescence temperature increases for the compound in hydrogen-bonding solvents, the observed process was considered to be N-inversion.²⁴² The contrary view²⁴³ that the process is ring inversion was challenged.²⁴⁴ This contrary view had arisen from consideration that the *N*-Me_{ax} \rightarrow *N*-Me_{eq} barrier should be lower than observed: it is now known that the observed process is *N*-Me_{eq} \rightarrow *N*-Me_{ax} and that the other half barrier is indeed lower.² A study²⁴⁵ of the ¹³C-NMR spectrum of *N*-methyl-2-oxa-3-azabicyclo[2.2.2]octane (**237**) gives ΔG^\ddagger of 14.9 \pm 0.1 kcal mol⁻¹ and variable temperature ¹H-NMR spectral studies on the deuterated 1,2-oxazine

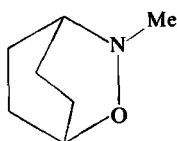
²⁴² F. G. Riddell, J. M. Lehn, and J. Wagner, *Chem. Commun.*, 1403 (1968).

²⁴³ I. J. Ferguson, A. R. Katritzky, and D. M. Read, *Chem. Commun.*, 255 (1975).

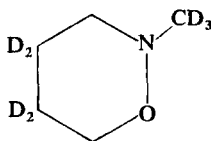
²⁴⁴ F. G. Riddell and H. Labaziewicz, *Chem. Commun.*, 766 (1975).

²⁴⁵ F. G. Riddell, E. S. Turner, and A. Boyd, *Tetrahedron* **35**, 259 (1979).

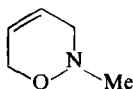
238 gives ΔH^\ddagger (eq \rightarrow ts) 15.1 ± 0.4 kcal mol $^{-1}$ and ΔS^\ddagger $+2.3 \pm 1.5$ kcal mol $^{-1}$ K $^{-1}$. The similarities in activation parameter confirm that the low temperature process is N-inversion.



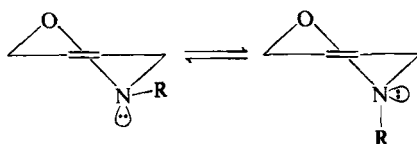
(237)



(238)



(239)



(240)

(241)

The low temperature $^1\text{H-NMR}$ spectra of 2-methyl-3,6-dihydro-2H-1,2-oxazine (**239**) gives a ΔG° favoring the $N\text{-Me}_{\text{eq}}$ of ~ 0.9 kcal mol $^{-1}$, which is significantly less than that for the tetrahydro-1,2-oxazine (≥ 1.9 kcal mol $^{-1}$).²⁴⁶ This is similar to the decrease in conformational free energy of a methyl substituent on going from methylcyclohexane (1.7 kcal mol $^{-1}$) to 4-methylcyclohexene (1.0 kcal mol $^{-1}$),²⁴⁷ and the equilibrium **240** \rightleftharpoons **241** may represent a balance between lone-pair- π -bond repulsion in **240** and lone-pair-lone-pair repulsions in **241**.²⁴⁶

2. Hexahydropyridazines and Tetrahydropyridazines

1,2-Dimethylhexahydropyridazine and related compounds can exist in eight conformations. It was recognized^{109,248,249} in 1971 that the barriers

²⁴⁶ R. A. Y. Jones, A. R. Katritzky, and S. Saba, *J. C. S. Perkin II*, 1737 (1974).

²⁴⁷ B. Rickborn and S.-Y. Lwo, *J. Org. Chem.* **30**, 2212 (1965).

²⁴⁸ R. A. Y. Jones, A. R. Katritzky, and R. Scattergood, *Chem. Commun.*, 644 (1971).

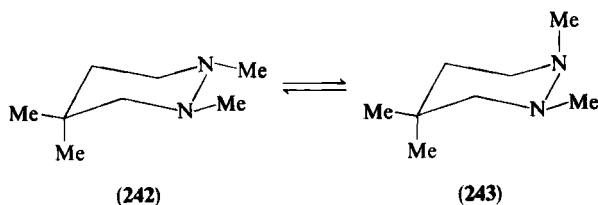
²⁴⁹ R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, *Chem. Commun.*, 644 (1971); V. J. Baker, A. R. Katritzky, J. P. Majoral, S. F. Nelsen, and P. J. Hintz, *J. C. S. Chem. Commun.*, 823 (1974); V. J. Baker, A. R. Katritzky, and J. P. Majoral, *J. C. S. Perkin II*, 1191 (1975).

separating these conformations are of two different types: "passing" barriers, where the process involved the eclipsing of two methyl groups, and "non-passing" barriers, which did not involve such eclipsing. The effects of such eclipsing are seen clearly in the conformational equilibria of the five-membered rings of 1,3,4-oxadiazolidines.²⁴⁹ This is conveniently illustrated in Fig. 11 (which is a modification^{12,250} of that originally given,^{108,248} clearer but topologically equivalent): passing processes involve crossing the vertical line (which also separates enantiomeric forms). (The increased energy of the passing barriers is due in part also to electronic interactions.²⁴³)

It is found that three types of barriers exist in cyclic hydrazines with six-membered rings: (a) high energy (12 kcal) passing barriers; (b) intermediate energy (10 kcal) for *ee* → *aa* ring inversions in saturated systems; (c) low energy (8 kcal) N-inversions without passing (this category also includes ring inversions of unsaturated rings).¹⁰⁹

The *N*-CH₂ protons will be equivalent in the ¹H-NMR spectrum of 1,2-dimethylhexahydropyridazine only if the two equivalent sets separated by the vertical line in Fig. 11 are interconverting rapidly on the NMR timescale. The *N*-Me group protons will, however, absorb as a singlet if rapid equilibration is occurring within a set, even though the sets are interconverting slowly on the NMR time scale.

The original ¹H-NMR work in this series²⁵¹ was reinterpreted¹⁰⁹ on the basis of the ¹³C-NMR spectra. *cis*-1,2,4,5-Tetramethylhexahydropyridazine shows a barrier of 12.6 kcal due to freezing of the passing interactions. 1,2,4,4-Tetramethylhexahydropyridazine (**242** ⇌ **243**) has only four conformers that do not possess β-diaxial methyl groups: the high-energy barrier is 11.5 kcal mol⁻¹ and the nonpassing ring inversion is frozen at lower temperatures with a barrier of 10.0 kcal mol⁻¹.



Unfortunately, although the equilibria for these substituted derivatives were interpreted correctly, for the parent 1,2-dimethylhexahydropyridazine the use of dipole-moment data led to erroneous results. It was first thought

²⁵⁰ S. F. Nelsen and G. R. Weisman, *J. Am. Chem. Soc.* **96**, 7111 (1974); **98**, 3281 (1976).

²⁵¹ J. E. Anderson, *J. Am. Chem. Soc.* **91**, 6374 (1969).

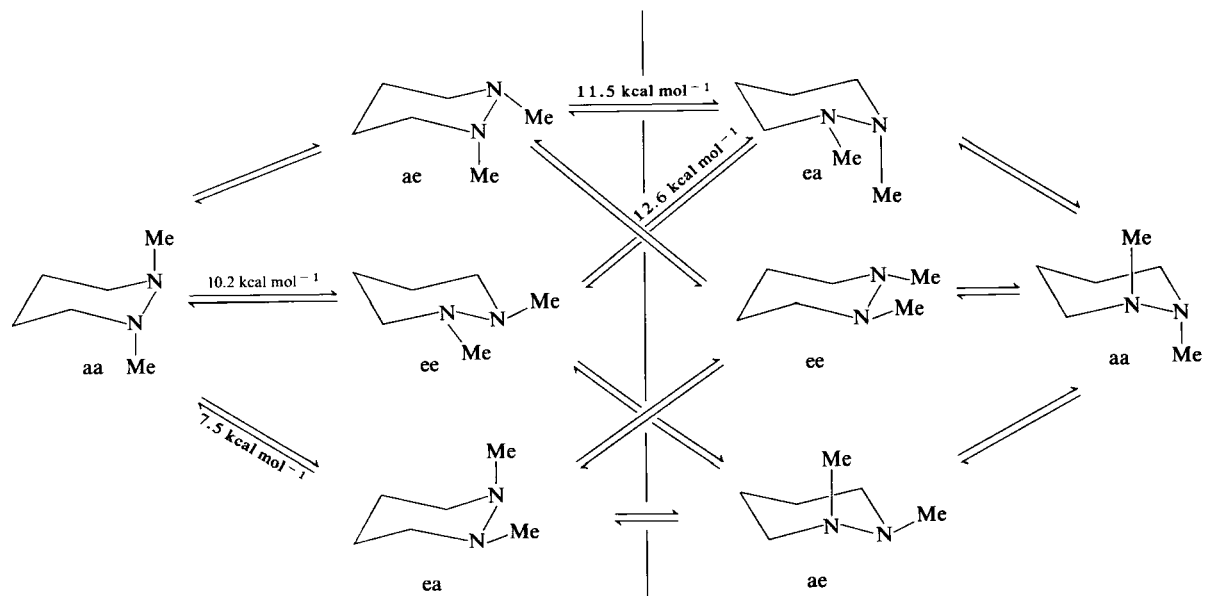


FIG. 11. Conformational interconversion for 1,2-dimethylhexahydropyridazine.²⁴⁹ (Reprinted with permission from Ref. 12. Copyright 1978 American Chemical Society.)

that the ae, ee, and aa* conformers were approximately equally populated,²⁵² and later¹⁰⁹ that the aa conformer actively predominated in the equilibrium. These conclusions, now known to be incorrect (see below), are ascribed to the assumptions and approximations inherent in the dipole-moment measurements, particularly in regard to the geometry of the model systems (X-ray work²⁵³ on **244** has shown MeNNMe and CH₂NNCH₂ torsional angles of 64° and 65°, respectively).



(244)

The advantages of low-temperature ¹³C-NMR study²⁵⁰ are shown by the results summarized in Table XVIII. Freezing out of the two slow passing processes does not affect the ¹³C-NMR spectrum, and the changes can be related directly to the nonpassing barriers. The chemical shifts of the ee and ea conformers may be assigned, using in particular, the γ_{ax}-effect (Section II,B,5). No lines were observed for the aa conformer. The percentage of ee in the ee ⇌ ea equilibrium was estimated at 57% at 50°C to 67% at -75°C, indicating the balance between the electronic destabilization of ee and the destabilization of ea by nonbonded interactions involving the axial methyl group. (In the corresponding 1,1,2-trimethylhexahydropyridazinium tetrafluoroborate equilibrium, the 2-methyl(ax) conformer is present as only 0.2–0.3% at -80°C, showing the stabilization of the 2-methyl(eq) conformer by alkylation.²⁵⁴)

The ΔG[‡] values for the ee ⇌ [ae ⇌ ea] nonpassing ring-inversion process and for the ae ⇌ ea nonpassing nitrogen inversion are given in Table XVIII. The slow passing nitrogen inversion barrier ee ⇌ ea was obtained on the bicyclic compound **244** [ΔG[‡]_{25°C} (ee → ea) 12.60 kcal mol⁻¹, (ea → ee) 12.71 kcal mol⁻¹]. The ΔG[‡] values are given in Fig. 11.

¹³C-NMR spectra were used to obtain further conformation equilibria in the hexahydropyridazine series. In the case of the two isomeric 1,2,3,6-tetramethylhexahydropyridazines only ae conformations **245** and **246** are detected,²⁵⁰ and the 1,6-diazabicyclo[4.4.0]decane strongly favors the ee conformation **247** [ΔG[°]₋₄₉ trans ⇌ cis > 2.4 kcal mol⁻¹].²⁵⁰ These results have been confirmed by photoelectron spectroscopy.¹⁵² The favoring of the

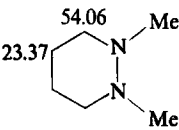
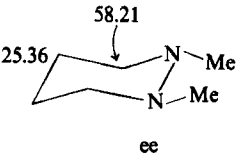
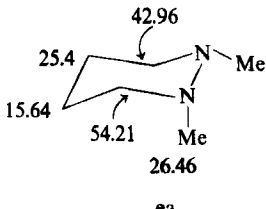
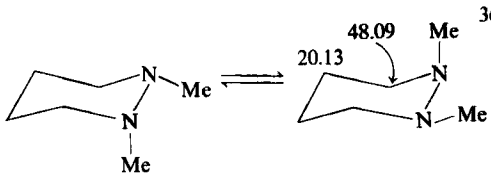
* ee, ea, aa, etc. refer to conformers shown in Fig. 11.

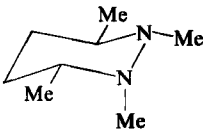
²⁵² R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, *J. C. S. Perkin II*, 34 (1972).

²⁵³ S. F. Nelsen, W. C. Hollinsed, and J. C. Calabrese, *J. Am. Chem. Soc.* **99**, 4461 (1977).

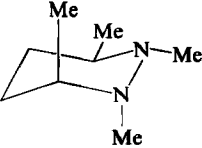
²⁵⁴ S. F. Nelsen and P. M. Gannett, *J. Am. Chem. Soc.* **103**, 3300 (1981).

TABLE XVIII
VARIABLE TEMPERATURE ^{13}C -NMR RESULTS FOR 1,2-DIMETHYLPYRIDAZINE²⁵⁰

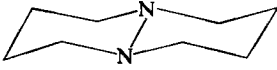
Temperature (°C)	Equilibria	^{13}C Chemical shifts
33	As in Fig. 11 (all passing inversions could be frozen out without effect on spectrum)	
-68	Freezing of $ae \rightleftharpoons ee$ ring inversion $ee \xrightleftharpoons[\text{inversion}]{\text{ring}} [ae \rightleftharpoons ea]$ $\Delta G^\ddagger_{-30^\circ} 10.30 \pm 0.07 \text{ kcal mol}^{-1}$	 ee
-121	Freezing of $ae \rightleftharpoons ea$ nitrogen inversion $\Delta G^\ddagger_{-100^\circ} 7.56 \pm 0.04 \text{ kcal mol}^{-1}$	 ea
-68 to -121	Between above two coalescences	



(245)



(246)



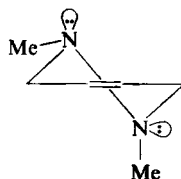
(247)

ee conformer over the ae conformer of 1,2-dimethylhexahydropyridazine by $0.4 \text{ kcal mol}^{-1}$ in solution is shown, by variable-temperature photoelectron spectroscopy, to increase to $1.20 \pm 0.08 \text{ kcal mol}^{-1}$ in the vapor phase.²⁵⁵

²⁵⁵ A. Schweig, N. Thon, S. F. Nelsen, and L. A. Grezzo, *J. Am. Chem. Soc.* **102**, 7438 (1980).

3. Tetrahydropyridazines and Hydropyridazines with Fused Rings

1,2-Dimethyl-1,2,3,6-tetrahydropyridazine exists exclusively in the ae conformation **248**.^{109,251} This is to be expected because the interactions involving the axial methyl group are now considerably less than that in ae 1,2-dimethylhexahydropyridazine.¹⁰⁹ The ¹H-NMR spectrum of 1,2,4,5-tetramethyl-1,2,3,6-tetrahydropyridazine also indicates the predominance of the ae conformer and shows ΔG^\ddagger for the passing interaction of 12.8 kcal mol⁻¹.¹⁰⁹



(248)

Alkylation of 1,2-dimethyl-1,2,3,6-tetrahydropyridazine, as in 1,1,2-trimethyl-1,2,3,6-tetrahydropyridazinium tetrafluoroborate, reduces the percentage of 2-methyl(ax) conformer to 3.5–5.5% at -80°C .²⁵⁴

The similarity in ΔG^\ddagger for the ae \rightleftharpoons aa nitrogen inversion process in 1,2-dimethylhexahydropyridazine and for the ae \rightarrow aa process in *trans*-1,2,3,6-tetramethylhexahydropyridazine (**245**) (ΔG^\ddagger 7.85 kcal mol⁻¹ at 25°C), in which the inversion involves NMe–CMe passing, supports²⁵⁶ the view²⁴³ (see above) that the difference between ΔG^\ddagger for the fast ea \rightleftharpoons aa and slow ee \rightleftharpoons aa nitrogen inversion is due in part to the differing electronic destabilizations in the transition states.

¹H-NMR spectra of **248**, which provide²⁵⁷ ΔG^\ddagger of ~ 12 kcal mol⁻¹ were shown¹⁰⁹ to be compatible with its existence in ae conformations. A range of bicyclic relatives have been studied²⁵⁸ by ¹³C-NMR spectroscopy and the results are shown in Table XIX. Comparison with the saturated analogs again shows a shift toward the ae conformations.

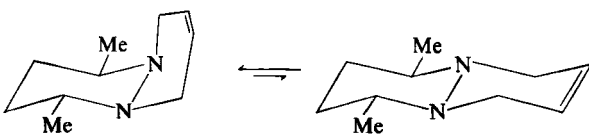
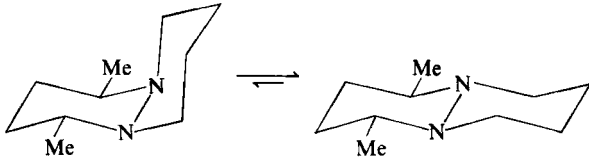
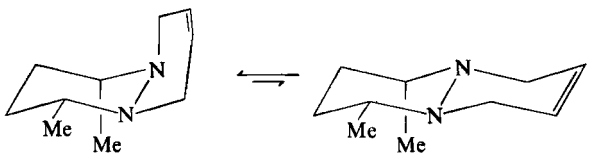
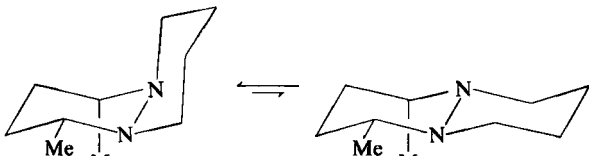
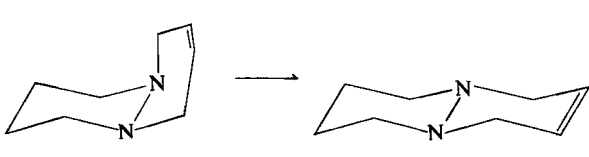
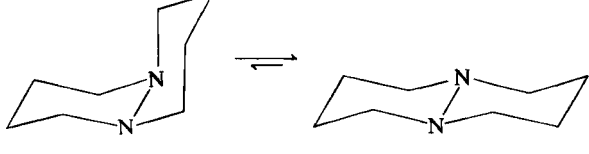
In the bicyclic systems ΔG^\ddagger values are greater than in the monocyclic analogs (e.g., ΔG^\ddagger 14.43 kcal mol⁻¹) for the ae \rightleftharpoons ee process in *trans*-2,5-dimethyl-1,6-diazabicyclo[4.4.0]decane, (depicted in Table XIX) inasmuch as nitrogen inversion and ring inversion are now coupled processes.

²⁵⁶ B. Price, I. O. Sutherland, and F. G. Williamson, *Tetrahedron* **22**, 3477 (1966).

²⁵⁷ B. Junge and H. A. Staab, *Tetrahedron Lett.*, 709 (1967).

²⁵⁸ S. F. Nelsen and E. L. Clennan, *J. Am. Chem. Soc.* **100**, 4004 (1978).

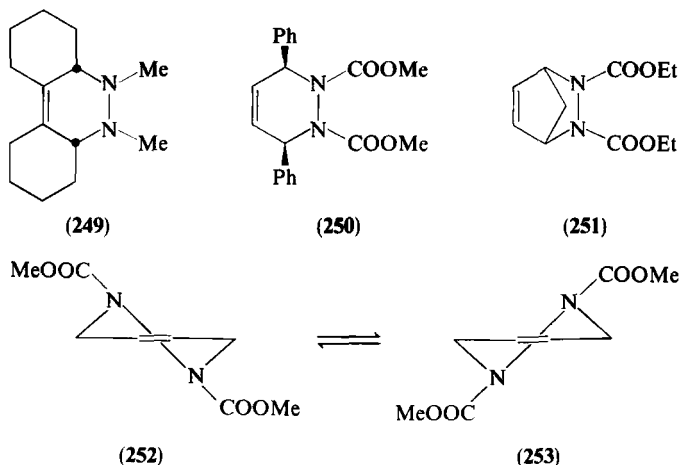
TABLE XIX
COMPARISON OF CONFORMATIONAL EQUILIBRIA IN 1,6-DIAZABICYCLO[4.4.0]DEC-3-ENES
AND IN 1,6-DIAZABICYCLO[4.4.0]DECANES²⁵⁸

Structure	ΔG_{25}° (kcal mol ⁻¹)
	+0.81
	-0.31
	Very positive
	+0.09
	-0.72
	Very negative

X-Ray studies²⁵² on the tetrahydropyridazine **249** (as in the crystal) show appreciable flattening of the nitrogen atoms and a decrease in the N—N bond length compared to **244**.

4. N-Acylhydropyridazines

The 1,2-dimethoxycarbonyl-1,2,3,6-tetrahydropyridazines and related systems exemplified by **250**^{259–265} are characterized by two conformational processes. Thus for **250**²⁵⁹ the rotational process about the N—COOMe bond is indicated by ¹H-NMR coalescence measurements to possess ΔG^\ddagger_3 14.8 kcal mol⁻¹, whereas ring inversion is characterized by a high-temperature spectral change, giving ΔG^\ddagger_{97} 18.9 kcal mol⁻¹. This interpretation has been confirmed²⁶³ by similar measurements on **251**, which give ΔG^\ddagger_c 13.7 \pm 0.5 kcal mol⁻¹, which can be due only to rotation about the NCOOEt bond. The unusually high energy barrier assigned to the ring inversion process **252** \rightleftharpoons **253** may be due to steric eclipsing of COOR groups in the transition state, entropic effects, or electronic effects, because ring inversion may occur with rotation about the N—N bond.²⁶⁴ This latter effect is supported by the high barrier to rotation (20–21 kcal mol⁻¹) about N—N



²⁵⁹ J. C. Breliere and J. M. Lehn, *Chem. Commun.*, 426 (1965).

²⁶⁰ R. Daniels and K. A. Roseman, *Chem. Commun.*, 429 (1966).

²⁶¹ R. Daniels and K. A. Roseman, *Tetrahedron Lett.*, 1335 (1966).

²⁶² B. H. Korsch and N. V. Riggs, *Tetrahedron Lett.*, 5897 (1966).

²⁶³ J. E. Anderson and J. M. Lehn, *Tetrahedron* **24**, 123 (1968).

²⁶⁴ J. E. Anderson and J. M. Lehn, *Tetrahedron* **24**, 137 (1968).

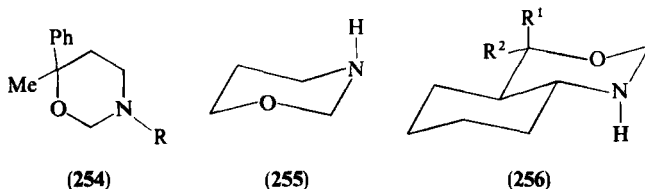
²⁶⁵ J. Firl, *Chem. Ber.* **102**, 2177 (1969).

bonds in tetraacylhydrazines.²⁶² The conformational free energy of 2-substituents in 1,2-dimethoxycarbonyl-1,2,3,6-tetrahydropyridazines have been estimated²⁶⁵ by ¹H-NMR spectroscopy (COOMe 1.7, CN 2.7, Ph 3.1, Me 3.3, Et 4.2, *i*Pr 4.6 kcal mol⁻¹).

D. 1,3-HETEROCYCLIC SYSTEMS

1. Tetrahydro-1,3-oxazines

a. *Tetrahydro-1,3-oxazine*. The conformational equilibria of tetrahydro-1,3-oxazines are dominated by the increased preference (related to piperidines) of the N-substituent for the axial position as a consequence of the generalized anomeric effect and the replacement of an axial CH bond by a heteroatom with an axial lone pair of electrons. The axial preference for *N*-H in tetrahydro-1,3-oxazines unsubstituted at nitrogen was recognized early²⁶⁶ from a comparison of J_{gem} values (Section II,B,2) in 6-methyl-6-phenyltetrahydro-1,3-oxazines [$J_{2\text{ax},2\text{eq}} -9.6$ Hz for **254** (R = Me), $J_{2\text{ax},2\text{eq}} -10.7$ Hz for **254** (R = H)]. In tetrahydro-1,3-oxazine itself, the low temperature ¹H-NMR spectrum (-80°C , CFC₃) showed $J_{2\text{eq},2\text{ax}} -10.1$ Hz, $J_{2\text{eq},\text{NH}} 2.9$ Hz and $J_{2\text{ax},\text{NH}} 13.1$ Hz, indicating the predominance of the axial *N*-H conformer **255**.²⁶⁷ Similar axial *N*-H preferences are shown by the bicyclic systems **256** [$J_{\text{gem}} -10.3$ Hz in **256** (R¹ = H, R² = Me), $J_{\text{gem}} -10.7$ Hz in **256** (R¹ = Me, R² = H)].²⁶⁸



Dipole-moment measurements indicate 62% *N*-H-axial for tetrahydro-1,3-oxazine and 74% *N*-H-axial for 5,5-dimethyltetrahydro-1,3-oxazine,²⁶⁹ but these estimates could well be low. The predominant *N*-H-axial conformation is clearly demonstrated by the IR spectrum in the first overtone *N*-H

²⁶⁶ Y. Allingham, R. C. Cookson, T. A. Crabb, and S. Vary, *Tetrahedron* **24**, 4625 (1968).

²⁶⁷ H. Booth and R. U. Lemieux, *Can. J. Chem.* **49**, 777 (1971).

²⁶⁸ Yu. Yu. Samitov, O. I. Zhuk, I. P. Boiko, B. V. Unkovskii, and Yu. F. Malina, *Zh. Org. Khim.* **10**, 1283 (1974).

²⁶⁹ A. R. Katritzky, M. Moreno-Mañas, A. C. Richards, A. J. Sparrow, and D. L. Trepanier, *J. C. S. Perkin II*, 325 (1973).

stretching region (Section II,E,2), which shows a single band with a very prominent Q branch at 6538 cm^{-1} .^{236,269}

b. *N-Alkyltetrahydro-1,3-oxazines*. Early work on tetrahydro-1,3-oxazines clearly showed the increased preferences of *N*-alkyl substituents, relative to piperidine derivatives, for the axial position, expected in part as a consequence of the generalized anomeric effect (Section I). However, the quantitative interpretation of the equilibria has not been simple until recently, when definitive ^{13}C -NMR data have become available.

Some of the trends indicated by the ^{13}C -NMR study⁹⁷ are summarized in Table XX. The conformers were readily recognized by means of γ -substituent effects (Section II,B,5). For the simple 3-alkyltetrahydro-1,3-oxazines, the slowing of ring-inversion processes are not detectable by the ^{13}C -NMR variable-temperature technique, and entries 1 and 5 show the axial preference for the 2-methyl and 2-ethyl derivatives with an increased

TABLE XX
 ^{13}C -NMR COALESCENCE DATA FOR TETRAHYDRO-1,3-OXAZINES⁹⁷

Entry	Tetrahydro-1,3-oxazine	ΔG° ^a	ΔG_c^\ddagger (N-Inversion) ^b	
			eq \rightarrow ts	ax \rightarrow ts
1		-0.10 ± 0.05	7.45	7.55
2		-0.10 ± 0.05	7.45	7.55
3		$+0.05$	7.63	7.58
4		-0.76	7.79	8.55
5		-0.50 ± 0.05	6.44	6.94

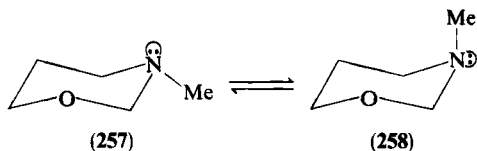
^a Negative value indicates *N*-CH₃ axial is preferred.

^b T_c -105 to -128°C.

axial preference for the latter. ΔG^\ddagger (N-inversion) values are reduced by the bulkier alkyl substituents (compare entries 1 and 5) as expected (Section I). The ΔG_c^\ddagger for ring inversion is higher ($10.0 \text{ kcal mol}^{-1}$) than for nitrogen inversion.²⁷⁰ For the 2,3-dialkyltetrahydro-1,3-oxazines, the equilibria are so heavily biased toward the 2e,3e and 2e,3a conformers, that no spectral changes corresponding to ring inversion are seen, whereas the spectra of 3,4-dialkyltetrahydro-1,3-oxazines at low temperatures exhibit peaks corresponding to both sets of conformers ($ee \rightleftharpoons ea \rightleftharpoons (aa \rightleftharpoons ae)$), as shown in Table XXI. Comparison of, for example, ΔG° for the ring inversion equilibrium in 2,3-dimethyltetrahydro-1,3-oxazines ($\Delta G^\circ > 2.0 \text{ kcal mol}^{-1}$) with that in 3,4-dimethyltetrahydro-1,3-oxazines ($\Delta G_c^\circ + 1.3 \text{ kcal mol}^{-1}$) shows the greater equatorial preference of C-2 Me than C-4 Me (Table XXI). Introduction of a 2- or a 4-methyl substituent has little effect on the barriers to nitrogen inversion (compare entries 1 and 2 and entries 1 and 3 in Table XX), whereas the 2-methyl group increases the equatorial preference of the N-substituent (compare entries 1 and 3, Table XX). The highest axial preference and barrier to nitrogen inversion is observed for the 2,3,4-trimethyl compound (entry 4, Table XX).

Ring-inversion barriers in tetrahydro-1,3-oxazines (Table XXI) decrease with increasing size of substituent. Inclusion of a 4-methyl substituent also decreases ΔG_c^\ddagger for the process.

Earlier $^1\text{H-NMR}$ work had been misleading. The $^1\text{H-NMR}$ spectrum of 3-methyltetrahydro-1,3-oxazine (**257** \rightleftharpoons **258**) shows at -145°C two *N*-Me singlets at δ 2.48 (major conformer) and δ 2.02 (minor conformer), which were originally assigned incorrectly to the equatorial and axial *N*-methyl conformers, respectively.²⁷⁰ The methyl group protons syn-axial to the oxygen atom are in fact deshielded so that the low-field singlet (major isomer) must be attributed to the axial *N*-methyl conformation. With this reversal of assignments, this $^1\text{H-NMR}$ work is consistent with 65% *N*-methyl axial conformer at -145°C (57% at 25°C).

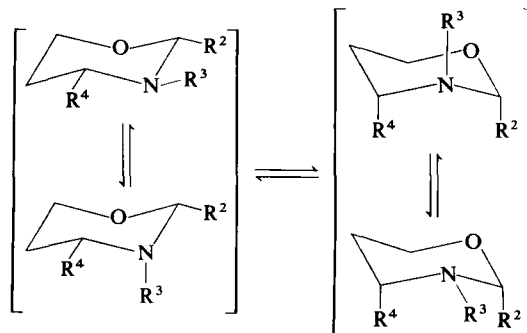


Dipole-moment measurements were interpreted as favoring the *N*-alkyl equatorial conformation for a range of *N*-alkyl tetrahydro-1,3-oxazines, giving 58% eq *N*-Me, 68% eq *N*-Et, 86% eq *N*-*i*Pr and $\sim 100\%$ eq *N*-*t*-Bu,²⁷¹ but these conclusions can no longer be regarded as reliable.

²⁷⁰ I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J. C. S. Perkin II*, 818 (1977).

²⁷¹ R. A. Y. Jones, A. R. Katritzky, and D. L. Trepanier, *J. Chem. Soc. B*, 1300 (1971).

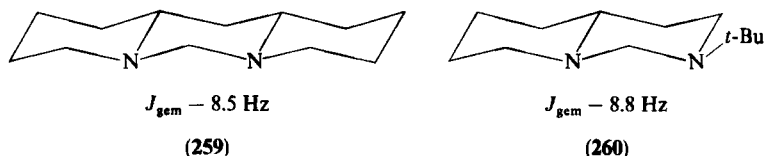
TABLE XXI
¹³C-NMR-DERIVED EQUILIBRIUM (ΔG_c°) AND KINETIC (ΔG_c^\ddagger) PARAMETERS FOR RING INVERSION IN
TETRAHYDRO-1,3-OXAZINES⁹⁷



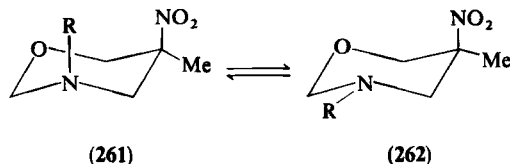
Compound			ΔG_c^\ddagger (kcal mol ⁻¹)		
R ²	R ³	R ⁴	ΔG_c° (kcal mol ⁻¹)	C-2—R _{ax} → transition state	C-2—R _{eq} → transition state
H	Me	H	—	—	10.0
Me	Me	H	> 2.0	—	—
H	Me	Me	+ 1.3	9.5	—
Me	Me	Me	> 2.0	—	10.0
H	Et	H	—	—	9.9
Me	Et	H	> 2.0	—	—
H	Et	Me	+ 0.67	9.21	—
Et	Et	H	> 2.0	—	9.88
iPr	Et	H	+ 1.1	8.6	9.7
H	iPr	H	—	—	9.5
Me	iPr	H	> 2.0	—	—
H	iPr	Me	+ 0.42	8.68	9.11

J_{gem} and Δ_{ac} measurements on 3-methyltetrahydro-1,3-oxazine in CF_2Cl_2 at -85°C indicated $60 \pm 10\%$ (based on Δ_{ac} measurements) and $40 \pm 10\%$ (based on J_{gem} measurements) axial *N*-methyl conformer.^{272,273} A later determination²⁶⁷ gave a J_{gem} of -9.5 Hz (rather than -8.9 Hz²⁷²), indicating $\sim 66\%$ axial *N*-methyl conformer (at -90°C).

The J_{gem} values for the NCH_2O protons in tetrahydro-1,3-oxazines have been criticized⁴⁴ as a valid probe for the conformational equilibria in such systems. The discussion in Section II,B,2 however points out that lone pair orientation should be the major (but not exclusive) factor affecting the magnitude of this parameter. The recently published ^1H -NMR J_{gem} data⁹⁶ on the 1,3-oxazines and the revised picture of the conformational equilibria (based on ^{13}C -NMR results rather than those based on dipole-moment measurements^{44,271}) now shows (Fig. 12) a much improved correlation for the plot of revised J_{gem} values against revised estimates of percentage axial lone pair, than the original plot.⁴⁴ The *tert*-butyl group is expected to cause flattening at the nitrogen atom and so will affect J_{gem} (this effect is shown by a comparison of J_{gem} in **259**¹³⁷ and **260**⁶⁰).



Dipole-moment measurements on some 3-alkyl-5-methyl-5-nitrotetrahydro-1,3-oxazines apparently indicate the predominance of the axial *N*-alkyl conformer **261** for the 3-methyl and 3-ethyl derivatives and the predominance of the equatorial *N*-alkyl conformer **262** for the corresponding *tert*-butyl and cyclohexyl derivatives.^{274,275} J_{gem} (Table XXII) and Δ_{ac} measurements²⁶⁶ (Sections II,B,1 and 2) support the predominant equatorial *N*-alkyl preference (**262**: $\text{R} = t\text{-Bu}$ and cyclohexyl), although Δ_{ac} was found to be concentration dependent.²⁷⁶ Comparison of the values of $J_{2\text{ax},2\text{eq}}$ in Table XXII with corresponding values for the locked and anancomeric



²⁷² F. G. Riddell and J. M. Lehn, *J. Chem. Soc. B*, 1224 (1968).

²⁷³ J. M. Lehn, P. Linscheid, and F. G. Riddell, *Bull. Soc. Chim. Fr.*, 1172 (1968).

²⁷⁴ D. Gürne and T. Urbanski, *J. Chem. Soc.*, 1912 (1959).

²⁷⁵ D. Gürne, L. Stefaniak, T. Urbanski, and M. Witanowski, *Tetrahedron, Suppl.* **6**, 211 (1964).

²⁷⁶ T. A. Crabb and S. I. Judd, *Org. Magn. Reson.* **2**, 317 (1970).

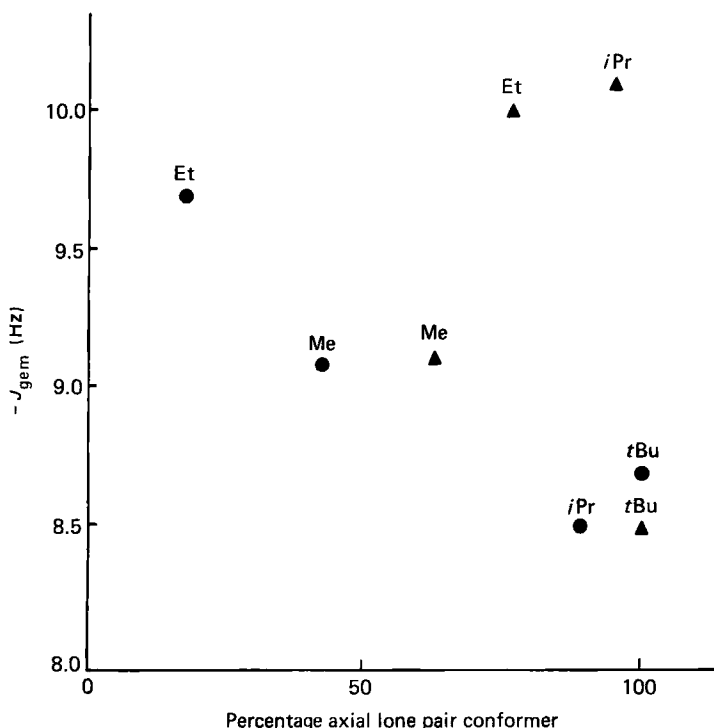


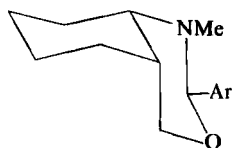
FIG. 12. Plots of $-J_{\text{gem}}$ against percentage axial lone-pair conformer in 3-alkyltetrahydro-1,3-oxazines. ●, values for percentage axial lone pair from dipole-moment data.⁴⁴ ▲, values for percentage axial lone pair from ^{13}C -NMR measurements.⁹⁶ J_{gem} for the *iPr* compound is now⁹⁶ given as -8.5 Hz, but no figure for percentage axial lone pair based on ^{13}C -NMR measurements is available; an estimate of 90% has been taken in the figure.

analog in Table V, however, indicates $\sim 64\%$ **262** ($\text{R} = \text{Me}$) \rightleftharpoons 36% **261** ($\text{R} = \text{Me}$) for the 3-methyl derivative and $\sim 50:50$ equilibrium mixture for the ethyl analog and apparently shows the increased axial preference for ethyl over methyl. The *cis*(4*a*-*H*,8*a*-*H*)-2-aryl-*N*-methylperhydrobenz[*d*][1,3]oxazine and the corresponding benz[*e*][1,3]oxazine adopt

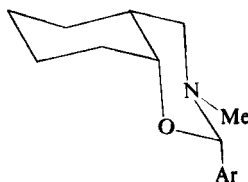
TABLE XXII
 J_{gem} VALUES IN 3-ALKYL-5-METHYL-5-NITRO-TETRAHYDRO-1,3-OXAZINES²⁶⁶

3-Substituent	% NR _{eq} conformation (262)	$J_{2\text{ax},2\text{eq}}$	$J_{4\text{ax},4\text{eq}}$
Me	~ 37	-8.6	-13.0
Et	~ 57	-9.0	-13.2
<i>iPr</i>	~ 17	-8.0	-12.4
<i>t</i> -Bu	~ 7	-7.7	-12.0

conformations **263** and **264**, respectively, reflecting the relative spatial requirements of the substituents attached to the bridgehead carbon atom.²⁷⁷ N- or O- inside/outside conformations have been assigned^{277a} to various cis-fused perhydrobenzo[*e*][1,3]oxazin-2-ones and -4-ones and perhydrobenzo[*d*][1,3]oxazin-2-ones. Bond lengths and angles have been determined on 2-(*p*-nitrophenyl)benzo[*d*] and -[*e*][1,3] oxazines.^{277b}

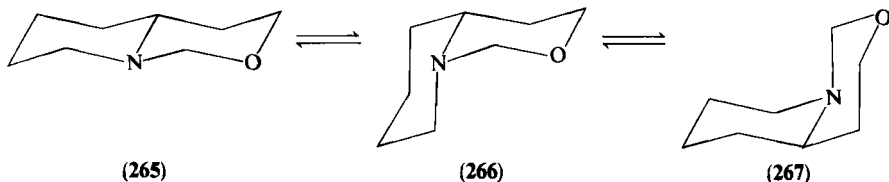


(263)



(264)

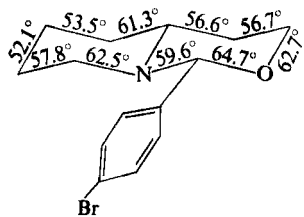
c. *Perhydropyrido*[1,2-*c*][1,3]oxazines. Perhydropyrido[1,2-*c*][1,3]-oxazine has three conformers: the trans-**265**, the O-inside cis-**266** and the O-outside cis-**267**. X-Ray measurements on the trans-fused hexahydro-*cis*-(1-*H*,4*a-H*)-1-*p*-bromophenyl-1*H*,3*H*-pyrido[1,2-*c*][1,3]oxazine are summarized with the structure **268** and indicate considerable puckering at the oxygen atom.²⁷⁸ Conformers **265** and **267** are destabilized by the generalized



(265)

(266)

(267)



(268)

Bond distances		Bond angles	
N—C-1	1.486 Å	N—C-1—O	109.3°
N—C-4a	1.486 Å	C-1—O—C-3	111.5°
C-1—O	1.421 Å	O—C-3—C-4	108.1°
O—C-2	1.452 Å	C-4—C-4a—N	109.8°
C-3—C-4	1.529 Å	C-4a—N—C-1	110.6°
C-4—C-4a	1.512 Å		

²⁷⁷ L. Gera, G. Bernáth, and P. Sohár, *Acta Chim. Acad. Sci. Hung.* **105**, 293 (1980).

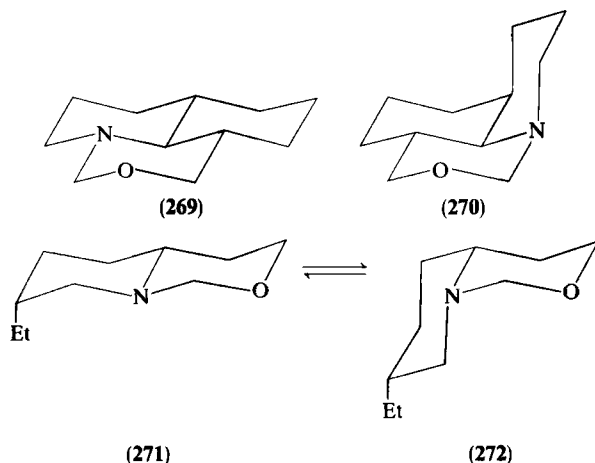
^{277a} G. Bernáth, F. Fülöp, G. Jerkovich and P. Sohár, *Acta Chim. Acad. Sci. Hung.*, **101**, 61 (1979); G. Stájer, A. E. Szabó, F. Fülöp and G. Bernáth, *Heterocycles*, **19**, 1191 (1982).

^{277b} G. Argay, A. Kálmán, F. Fülöp, and G. Bernáth, *Acta Chim. Acad. Sci. Hung.* **109**, 39 (1982).

²⁷⁸ A. Griffiths, *J. Cryst. Mol. Struct.* **3**, 349 (1973).

anomeric effect; **267** also involves three gauche-butane interactions. Conformer **266** is favored by the generalized anomeric effect but is destabilized by two gauche-butane interactions and one interaction involving the C-8 methylene and the oxygen atom. This latter interaction is less than the gauche-butane interaction, and so **266** is the favored cis conformation [compare conformers of *cis*-decahydroquinoline: **152** and **154** favored over **153** and **155** (Section III,B,1)]. Thus **267** should make no significant contribution to the equilibrium, and although the trans conformer **265** is expected to be favored, the equilibrium should contain a higher proportion of cis conformer **266** than in the quinolizidine equilibrium $\mathbf{179} \rightleftharpoons \mathbf{180} \rightleftharpoons \mathbf{181}$ (Section II,B,3).

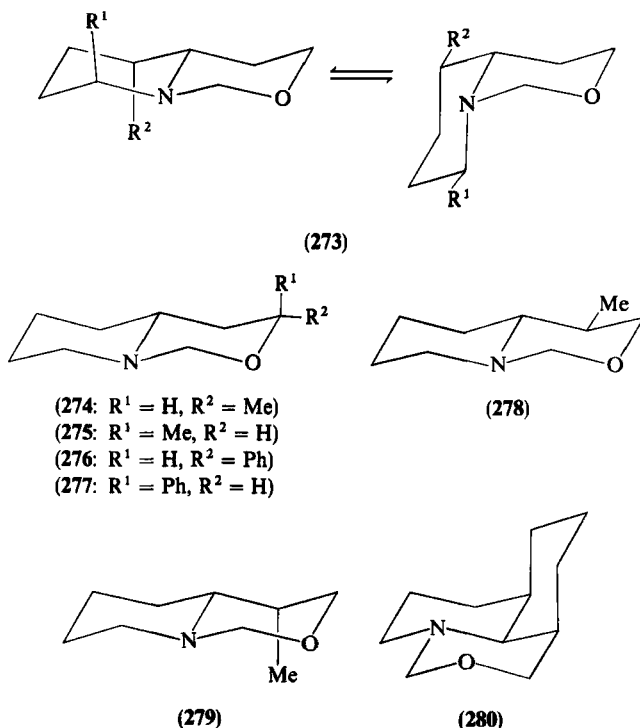
The ^1H -NMR spectra of perhydropyrido[1,2-*c*][1,3]oxazines and Bohlmann-band measurements (Section II,E,1) show the predominance of the trans-fused conformer **265**,¹³⁵ and comparison of ^1H -NMR chemical shifts in the locked perhydropyrido[3,2,1-*ij*][3,1]benzoxazines **269** and **270**,⁴⁵ taken as models for the trans- and cis-fused conformers, indicates $\sim 90\%$ **265** in the equilibrium at 25°C ($\Delta G^\circ \sim 1.3 \text{ kcal mol}^{-1}$). This is lower than that ($\Delta G^\circ 2.6 \text{ kcal mol}^{-1}$) for the corresponding quinolizidine equilibrium. This estimate is consistent with the results of dipole moments, which indicate predominantly trans conformer,⁶¹ and of a low-temperature ^1H -NMR study of *cis*(4*a*-*H*,7-*H*)-7-ethylperhydropyrido[1,2-*c*][1,3]oxazine ($\mathbf{271} \rightleftharpoons \mathbf{272}$),⁶¹ which showed $70\% \mathbf{272} \rightleftharpoons 30\% \mathbf{271}$ at -90°C . Assuming that the entropy difference between the conformers is small, then ΔG_{25}° of $-0.34 \text{ kcal mol}^{-1}$ may be estimated (63% cis conformer). This is in agreement with the predicted position of equilibria, assuming the conformational free energy of the 3-methyl group in piperidine ($\Delta G^\circ 1.51 \text{ kcal mol}^{-1}$,¹⁶⁹ Table XIII) to be approximately equal to that of the ethyl group in $\mathbf{271} \rightleftharpoons \mathbf{272}$. (ΔG° predicted $1.30 - 1.51 = -0.21 \text{ kcal mol}^{-1}$, 58% cis conformer).



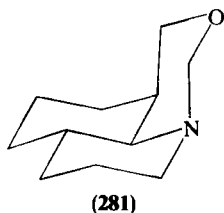
Ring-A methyl-substituted perhydropyrido[1,2-*c*][1,3]oxazines carrying axial methyl groups in the trans-fused conformation (**273**: $R^1 = H$, $R^2 = Me$ and **273**: $R^1 = Me$, $R^2 = H$) all adopt a position of conformational equilibrium similar to **271** \rightleftharpoons **272**.¹³⁵

The 3-methyl- and 3-phenylperhydropyrido[1,2-*c*][1,3]oxazines all adopt the trans-fused conformation (**274–277**).¹³⁵ The two 4-methyl derivatives **278** and **279** also adopt the trans conformation ($J_{gem} -7.8$ Hz in both isomers) but **279** shows an enhanced Δ_{ae} (0.87 ppm) (cf. 0.59 ppm in **278**) which cannot be due to changes in cis \rightleftharpoons trans conformational equilibria.²⁷⁹

The conformations of tri- and tetracyclic compounds containing the perhydropyrido[1,2-*c*][1,3]oxazine system have been determined by ¹H-NMR spectroscopy. The four perhydropyrido[3,2,1-*ij*][3,1]benzoxazines **269**, **270**, **280**, and **281** have been isolated, and the O-outside cis-conformational analog of **266**, which has not been observed in the bicyclic series, was shown to possess the same J_{gem} (-7.5 Hz) for the NCH_2O protons as that of the

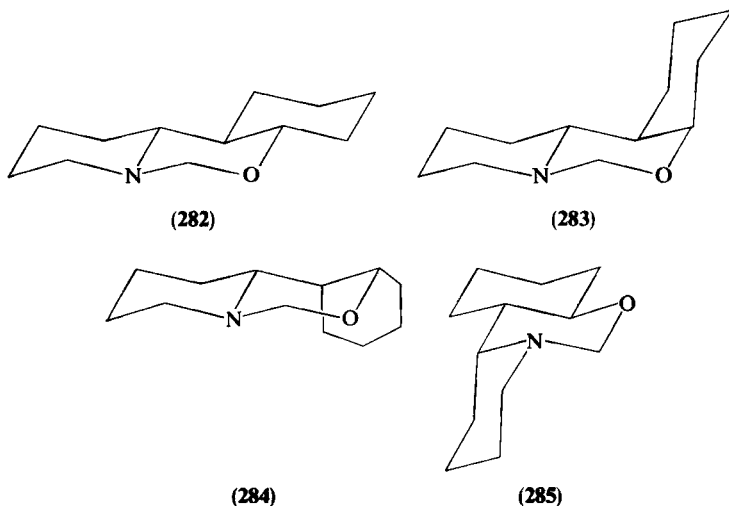


²⁷⁹ T. A. Crabb, P. J. Chivers, E. R. Jones, and R. F. Newton, *J. Heterocycl. Chem.* **7**, 635 (1970).



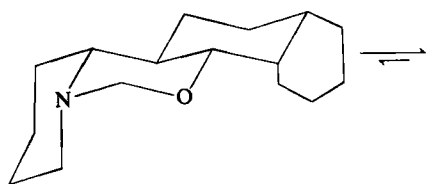
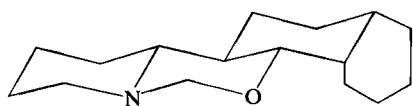
trans conformer **269**, which was expected because both possess the parallel nitrogen lone-pair $\text{NCH}_{\text{ax}}\text{O}$ geometry.⁴⁵

Three of the four diastereomeric perhydrobenzo[*e*]pyrido[1,2-*c*][1,3]oxazines adopt trans A-B conformations **282**–**284**, the remaining isomer adopting the cis A-B conformation **285** rather than the alternative trans A-B

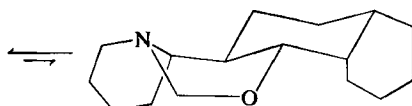
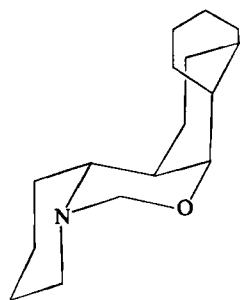
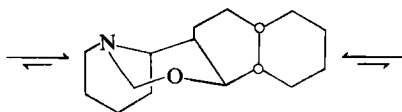
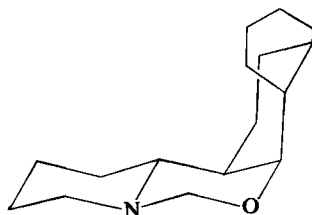


boat B ring.⁴⁶ Seven of the 16 possible diastereomeric perhydronaphthaleno-[3,4-*e*]pyrido[1,2-*c*][1,3]oxazines have been isolated.²⁸⁰ Each of these (**286**–**292**) may adopt a trans-fused (**286-t**–**292-t**) and two cis-fused conformations (**286-c**₁–**292-c**₁) and (**286-c**₂–**292-c**₂). ¹H-NMR (Sections II,B,1 and 2) and IR (Section II,E,1) spectroscopic studies indicate the predominant existence of the isomers in conformations **286-t**, **287-c**₂, **288-c**₂, **289-t**, **290-t**, **291-t**, and **292-c**₂.²⁸⁰ Boat conformations are disfavored and 1,3-syn-axial interactions markedly disfavor **287-c**₁, **287-t**, **289-c**₁, **290-c**₁, and **291-c**₂.

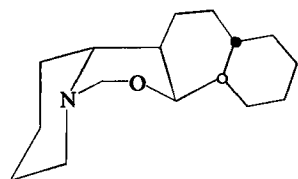
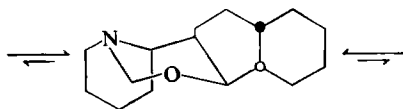
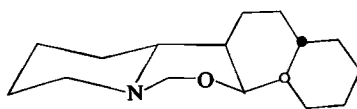
²⁸⁰ T. A. Crabb and J. S. Mitchell, *Org. Magn. Reson.* **16**, 141 (1981).

(286)-c₁

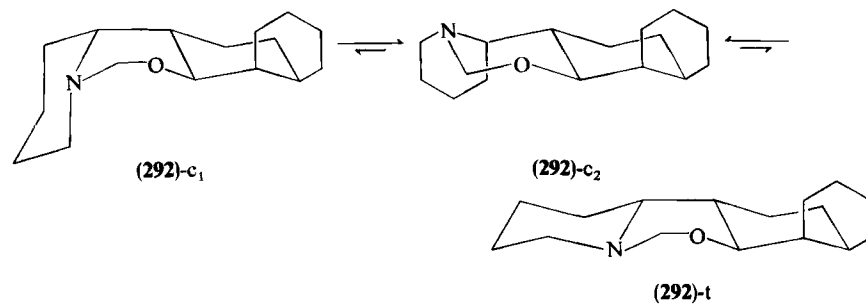
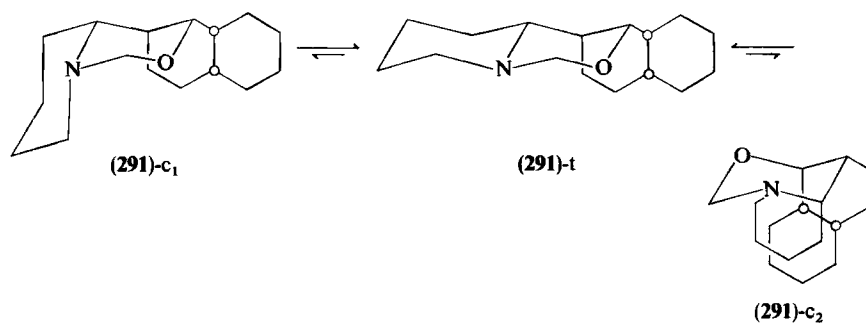
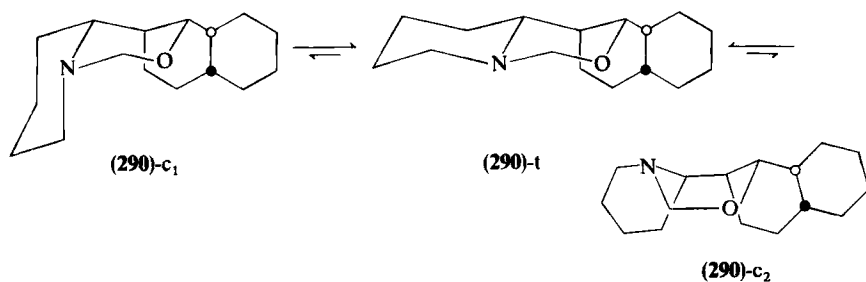
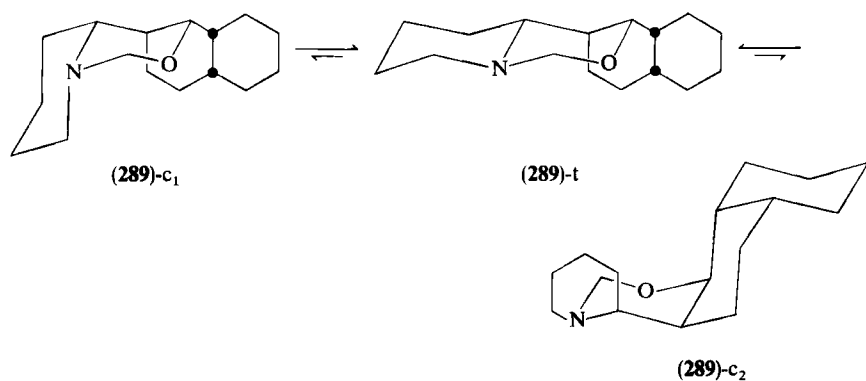
(286)-t

(286)-c₂(287)-c₁(287)-c₂

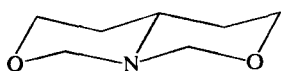
(287)-t

(288)-c₁(288)-c₂

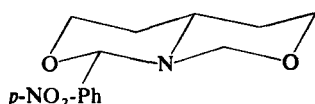
(288)-t



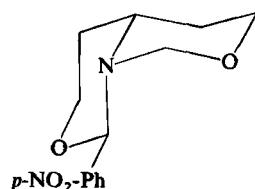
Perhydro[1,3]oxazino[3,4-*c*][1,3]oxazine and its (1-*H*,4*a*-*H*)-1-*p*-nitrophenyl derivative adopt the trans-fused conformations **293** and **294**, whereas the epimeric 1-*p*-nitrophenyl derivative prefers the cis-fused conformation **295**.²⁸¹



(293)

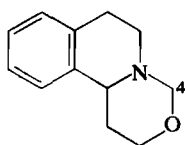


(294)

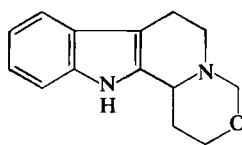


(295)

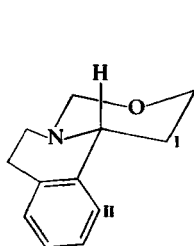
d. *Benzo Derivatives of Perhydropyrido[1,2-*c*][1,3]oxazine*. In contrast to perhydropyrido[1,2-*c*][1,3]oxazine, which adopts preferentially the trans-fused conformation **265** ($\Delta G_{25^\circ}^\circ \sim 1.3 \text{ kcal mol}^{-1}$), 1,6,7,11*b*-tetrahydro-2*H*,4*H*-[1,3]oxazino[4,3-*a*]isoquinoline (**296**)²⁸² and 1,6,7,12*b*-tetrahydro-2*H*,4*H*-[1,3]oxazino[3',4':1,2]pyrido[3,4-*b*]indole (**297**)²⁸³ adopt the O-inside cis conformation e.g., **299** (R = H) for **296** [$J_{\text{gem}} \text{NCH}_2\text{O} - 10.2 \text{ Hz}$, $\Delta_{\text{ae}} 0.19 \text{ ppm}$ (see Sections II,B,1 and 2)]. The alternative trans conformation **298** is destabilized by the generalized anomeric effect, the close approach



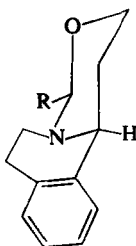
(296)



(297)



(298)



(299)

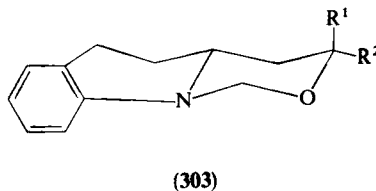
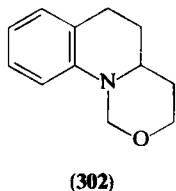
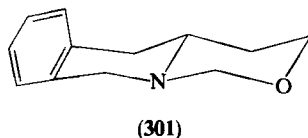
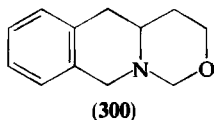
²⁸¹ T. A. Crabb and M. J. Hall, *J. C. S. Perkin II*, 1379 (1973).

²⁸² T. A. Crabb and R. F. Newton, *Tetrahedron Lett.*, 3361 (1971).

²⁸³ T. A. Crabb and J. S. Mitchell, *J. Heterocycl. Chem.* **8**, 721 (1971).

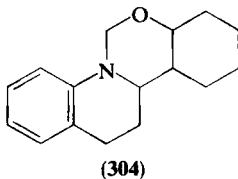
of C-1-H₂ and C-11-H, and ring-fusion strain,²⁸⁴ which are relieved in the cis conformer. The 4-aryl-substituted derivative also adopts the O-inside cis conformation **299** (R = aryl).²⁸⁵

The trans-fused conformation **301** of 3,4,11,11a-tetrahydro-1*H*,6*H*-[1,3]oxazino[3,4-*b*]isoquinoline (**300**) is destabilized only by the generalized anomeric effect, the peri-type interaction present in **298** being absent, and is accordingly adopted.^{282,284}



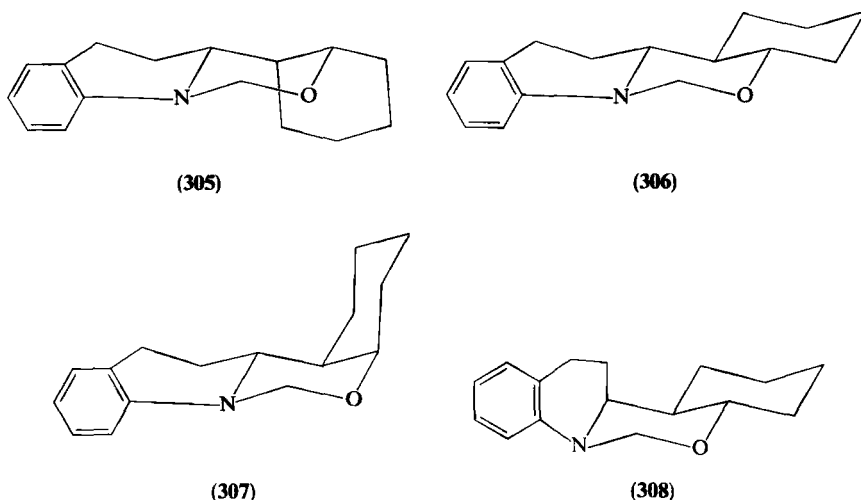
In the trans-fused conformation **303** (R¹ = R² = H) adopted by 4,4*a*,5,6-tetrahydro-1*H*,3*H*-[1,3]oxazino[3,4-*a*]quinoline (**302**), the nitrogen lone pair is able to overlap with the π orbitals of the aromatic ring, and this gives rise to a more negative value of J_{gem} (−10.5 Hz) than in **265** (J_{gem} −8.0 Hz) (Section II,B,2), but the trans-fused conformation is indicated by the large Δ_{ac} (NCH₂O) of 1.05 ppm (Section II,B,1). The trans-fused conformations **303** (R¹ = H, R² = Me) and **303** (R¹ = Me, R² = H) are also adopted by the two 3-methyl derivatives.⁶⁴

Of the four diastereomeric 8,9,10,11,11*a*,11*b*,12,13-octahydro-7*aH*-quino[1,2-*c*][1,3]benzoxazines (**304**), three prefer the trans-fused conformations **305**–**307**. The overlap of the nitrogen lone-pair orbital with the aromatic ring affects the J_{gem} and Δ_{ac} values of the NCH₂O protons in these isomers (Sections II,B,1 and 2), and the Bohlmann absorption (Section II,E,1) is no



²⁸⁴ T. A. Crabb, J. S. Mitchell, and R. F. Newton, *J. C. S. Perkin II*, 370 (1971).

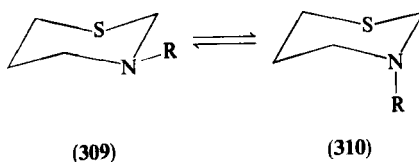
²⁸⁵ T. A. Crabb and J. S. Mitchell, *Org. Magn. Reson.* **8**, 258 (1976).



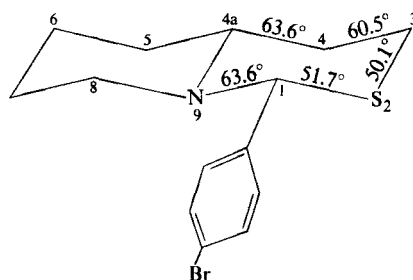
longer observed. J_{gem} in the fourth isomer is larger than that in **305–307**, indicating the cis-fused conformation **308**, in which the lone pair is orthogonal to the aromatic ring orbitals. These conformations are confirmed by UV absorption measurements.⁶⁴

2. Tetrahydro-1,3-thiazines

a. *Geometry.* Strain-minimization techniques³³ (see Section II,A and Fig. 2) applied to tetrahydro-1,3-thiazine (**309** \rightleftharpoons **310**) suggests puckering in the vicinity of the sulfur atom and flattening at the nitrogen atom resulting from the long C—S bond and small C—S—C bond angle. This geometry has been confirmed by an X-ray study on perhydro-*cis*-(1-*H*,4*a*-*H*)-1-*p*-bromophenylpyrido[1,2-*c*][1,3]thiazine (**311**).²⁸⁶ The dihedral angles show the increased puckering around the sulfur atom (51.7° and 50.1°), compared to those (64.7° and 62.7°) around oxygen in **268**.



²⁸⁶ A. Griffiths, *J. Cryst. Mol. Struct.* **3**, 357 (1973).



(311)

Bond distances		Bond angles	
N—C-1	1.479 Å	N—C-2—S	112.6°
N—C-4a	1.467 Å	C-1—S—C-3	97.1°
C-1—S	1.836 Å	S—C-3—C-4	111.7°
S—C-2	1.813 Å	C-3—C-4—C-4a	113.0°
C-3—C-4	1.488 Å	C-4a—N—C-1	111.4°
C-4—C-4a	1.510 Å		

b. *Monocyclic Compounds.* In tetrahydro-1,3-thiazine, the predominance of the *N*-H axial conformer **310** ($R = H$) is shown by measurements on the first overtone *N*-H absorption in the IR, and dipole-moment measurements indicated $\sim 22\%$ of the equatorial conformer **309** ($R = H$).^{236,270}

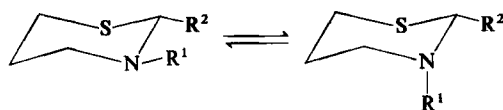
For 3-methyl- and 3-ethyltetrahydro-1,3-thiazine, reliable parameters on which to base an estimate of the position of conformation equilibria $\mathbf{309} \rightleftharpoons \mathbf{310}$ have recently become available²⁸⁷ based on ^{13}C -NMR parameters (Table XXIII). For the *N*-methyl derivative, the ΔG_c° for the equilibrium $\mathbf{309}$ ($R = \text{Me}$) \rightleftharpoons $\mathbf{310}$ ($R = \text{Me}$) of $-0.7 \text{ kcal mol}^{-1}$ shows a greater axial preference for the methyl group than in *N*-methyltetrahydro-1,3-oxazine ($\Delta G_c^\circ - 0.1 \text{ kcal mol}^{-1}$). The introduction of a 2-alkyl group increases significantly the predominance of the *N*-alkyl conformer (Table XXIII).

In the 2,3-dialkyltetrahydro-1,3-thiazines, the C-equatorial conformers always predominate; however an increase in the proportion of 2-axial conformers is observed with increasing size of the 2-substituent (see Table XXIV^{287,288} for the 3-ethyl-2-alkyltetrahydro-1,3-thiazines). This has been explained in terms of an increase in interaction between the 2-equatorial substituent and the *N*-alkyl group because flattening at the nitrogen atom

²⁸⁷ A. R. Katritzky, V. J. Baker, F. M. S. Brito-Palma, I. J. Ferguson, and L. Angiolini, *J. C. S. Perkin II*, 1746 (1980).

²⁸⁸ L. Angiolini, A. R. Katritzky, and D. M. Read, *Gazz. Chim. Ital.* **106**, 111 (1976).

TABLE XXIII
¹³C-NMR-DERIVED EQUILIBRIUM (ΔG_e°) AND KINETIC (ΔG_c^\ddagger) PARAMETERS FOR THE
 N-INVERSION PROCESS IN TETRAHYDRO-1,3-THIAZINES²⁸⁷



Compound		$\Delta G_c^\ddagger^{b,c}$	
R ¹	R ²	$\Delta G_e^\circ^{a,c}$	$\Delta G_c^\ddagger^{b,c}$
		NR _{eq} ¹ → transition state	NR _{ax} ¹ → transition state
Me	H	-0.7	6.9
Me	Me	< -2.0	—
Et	H	-0.8	6.0
Et	Et	< -2.0	—
Et	iPr	< -2.0	—

^a ΔG_e° values ± 0.1 kcal mol⁻¹.

^b ΔG_c^\ddagger values ± 0.5 kcal mol⁻¹.

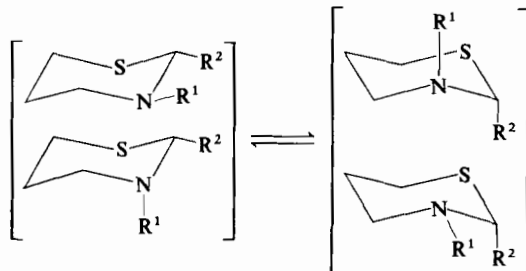
^c T_c values from -132 to -115°C.

(see X-ray results described above) increases the importance of such an interaction.²⁸⁷

Ring-inversion barriers (Table XXIV)^{287,288} decrease with increasing size of the *N*-substituent. For the 3-ethyl-2-alkyltetrahydro-1,3-thiazines, ΔG_c° for the ring-inversion process decreases along the series 2-methyl-, 2-ethyl-, 2-isopropyl- (Table XXIV). Dipole-moment measurements on a series of 3-alkyltetrahydro-1,3-thiazines²⁸⁸ are now considered to be unreliable as a quantitative guide to conformer proportions.

c. *Polycyclic Derivatives.* The greater tendency for an *N*-alkyl group to be axial in the 1,3-thiazine as compared to the 1,3-oxazine series is also reflected in the bicyclic analogs **312** \rightleftharpoons **313**.¹³⁶ The value of ΔG_{25}° for the equilibrium **312** \rightleftharpoons **313** is ~ 0.6 kcal mol⁻¹ compared to ~ 1.3 kcal mol⁻¹ for the corresponding perhydropyrido[1,2-*c*][1,3]oxazine equilibrium (**265** \rightleftharpoons **266**). These differences are also confirmed by dipole-moment measurements on the two systems⁶¹ and by the positions of conformational equilibria in alkyl-substituted derivatives. Thus in the ¹H-NMR spectrum of *cis*-(4*a*-H, 7-*H*)-7-ethylperhydropyrido[1,2-*c*][1,3]thiazine **314** \rightleftharpoons **315** only the *cis*-fused conformer **315** can be detected,¹⁰¹ whereas the corresponding oxazine exists in solution at 25°C as $\sim 63\%$ *cis*-fused conformer **272** in equilibrium with $\sim 37\%$ *trans*-fused conformer **271**. Other ¹H-NMR measurements¹³⁶ indicate the expected deviations from chair geometry. The low-temperature ¹³C-NMR spectrum of perhydropyrido[1,2-*c*][1,3]thiazine in CS₂-THF-*d*₈

TABLE XXIV
EQUILIBRIUM (ΔG_c°) AND KINETIC (ΔG_c^\ddagger) PARAMETERS FOR RING INVERSION IN TETRAHYDRO-1,3-THIAZINES²⁸⁷



Compound		ΔG_c^\ddagger (kcal mol ⁻¹) ^{b,c}			
R ¹	R ²	ΔG_c° (kcal mol ⁻¹) ^{a,c}	C-2—R _{eq} conformer → transition state		C-2—R _{ax} conformer → transition state
Et	Me	+0.8	10.1	—	9.3
Et	Et	+0.5	10.0	—	9.5
Et	iPr	+0.4	9.8	—	10.2
iPr	H	—	—	8.9	—
Et	H	—	—	9.8 ²⁸⁸	—

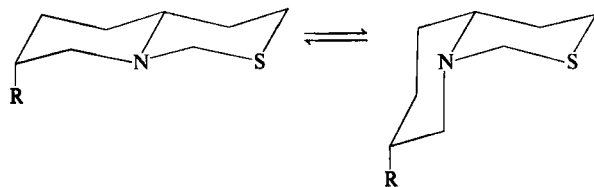
^a $\Delta G^\circ \pm 0.1$ kcal mol⁻¹.

^b $\Delta G^\ddagger \pm 0.5$ kcal mol⁻¹.

^c T_c — 70 to — 60°C.

(1:1) at -75°C shows 64% trans-fused conformer **312** in equilibrium with 36% S-inside cis conformer **313**.¹⁰¹

Following the trend observed for the oxazine analog **296**, the fusion of a benzene ring onto the $[f]$ position of perhydropyrido[1,2- c][1,3]thiazine, as in 1,6,7,11*b*-tetrahydro-2*H*,4*H*-[1,3]thiazino[4,3- a]isoquinoline **316**, pushes the equilibrium almost exclusively to the S-inside cis conformation **317**.²⁸⁴

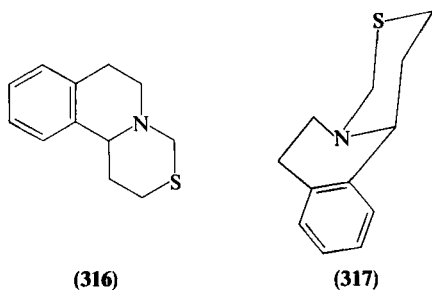


(312: R = H)

(313: R = H)

(314: R = Et)

(315: R = Et)

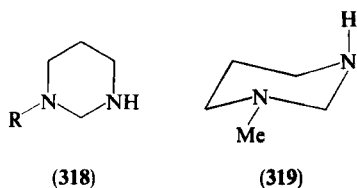


(316)

(317)

3. Hexahydropyrimidines

a. *N*-Alkylhexahydropyrimidines. The predominance of the axial *N*-H conformer (**319**) of 1-methylhexahydropyrimidine (**318**: R = Me) is demonstrated by IR measurements in the first overtone ν_{N-H} region.^{236,269} This conclusion is supported by the large vicinal coupling constant (13.0 Hz) between the *N*-H and 2(ax)-H protons and by the value (-11.3 Hz) of $J_{2ax,2eq}$ in the ^1H -NMR spectrum (CDCl_3 , room temperature).²⁶⁷ Dipole moment

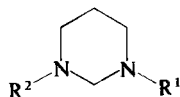


(318)

(319)

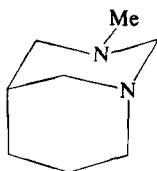
measurements on 1-*tert*-butylhexahydropyrimidine (**318**: R = *t*-Bu) indicate 66% *N*-H axial conformation,²³⁶ but this estimate could be low.

b. *N,N*-Dialkylhexahydropyrimidines Unsubstituted at C-2. The position of conformational equilibrium in *N,N*-dimethylhexahydropyrimidines (**320**: R¹ = R² = Me) has been studied using a variety of techniques and the results are summarized in Table XXV.

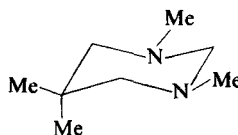


(320)

The definitive work is by ¹³C-NMR spectroscopy: both conformers were detected²⁸⁹ at -150°C and the ae conformer **321** was identified on the basis of the upfield (γ_{ax}) shift of the NCH₃ resonance (Section II,B,5). The results show the predominance of ee conformation **322** and are in line with the estimates based on dipole-moment measurements²⁹⁰ and J_{gem} comparisons with model compounds²⁹¹ (**323** model for **321** and **324** model for **322**). Calculation of the equilibrium position from comparison of the chemical shift of the 2(ax) proton with the values in **323** and **324** is also in agreement with the predominance of **322**,²⁹² but a similar exercise²⁹¹ based on Δ_{ae} measurements favors the ae conformation **321**; such chemical shift estimates are sensitive to the effect of the 5-substituents on the chemical shifts.²⁷⁹



(323)



(324)

Estimates of the percentage ee conformation in other *N,N*-dialkylhexahydropyrimidines are given in Table XXVI. Some disagreement exists between the positions of equilibria for the *N,N*-diisopropylhexahydropyrimidine based on dipole moment and on ¹H-NMR chemical-shift measurements but in this case the higher (dipole moment) value is probably more representative of the true state of the equilibrium.

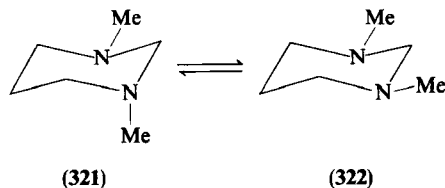
²⁸⁹ A. R. Katritzky, V. J. Baker, I. J. Ferguson, and R. C. Patel, *J. C. S. Perkin II*, 143 (1979).

²⁹⁰ R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc. B*, 131 (1970).

²⁹¹ F. G. Riddell and D. A. R. Williams, *Tetrahedron Lett.*, 2073 (1971).

²⁹² E. L. Eliel, L. D. Kopp, J. E. Dennis, and S. A. Evans, Jr., *Tetrahedron Lett.*, 3409 (1971).

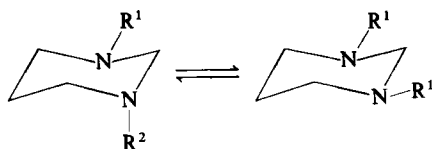
TABLE XXV
SUMMARY OF PUBLISHED WORK ON THE POSITION OF CONFORMATIONAL EQUILIBRIA IN
N,N-DIMETHYLHEXAHYDROPYRIMIDINES



Solvent	Eq-eq conformation (322) (%)	Method	Reference	Section of this review
Cyclohexane, 25°C	56	Dipole moments	290	II,D
CF ₂ Cl ₂ -(CD ₃) ₂ CO at -150°C	88 (estimated 70 at 25°C)	¹³ C NMR	289	II,B,5
CH ₂ Cl ₂	50	¹ H NMR [comparison of δ 2(ax)-H with those in model systems]	292	II,B,1
CH ₂ Cl ₂ , 33.5°C	60 ^a	¹ H NMR (comparison of <i>J</i> _{2ax,2eq} with those in model systems)	291	II,B,2
CH ₂ Cl ₂ , 33.5°C	42 ^a	¹ H NMR (comparison of Δ _{2ax,2eq} values with those in model systems)	291	II,B,1

^a Estimate based on *J* and Δ values for 1,3,5-trimethylhexahydropyrimidine.

TABLE XXVI
SUMMARY OF PUBLISHED WORK ON THE POSITION OF CONFORMATIONAL
EQUILIBRIA IN *N,N*-DIALKYLHEXAHYDOPYRIMIDINES



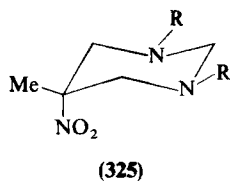
Compound	Eq, eq conformation (%)	Method	Reference
$R^1 = t\text{-Bu}, R^2 = \text{Me}$	69	Dipole moment ^a	289
$R^1 = t\text{-Bu}, R^2 = \text{Et}$	75	Dipole moment ^a	289
$R^1 = R^2 = \text{Et}$	59	Dipole moment ^a	289
	72	¹ H-NMR chemical shifts ^b	292
$R^1 = t\text{-Bu}, R^2 = i\text{Pr}$	100	Dipole moment ^a	289
	91	Dipole moment ^a	289
$R^1 = R^2 = i\text{Pr}$	80	¹ H-NMR chemical shifts ^b	292

^a Dipole-moment measurements refer to cyclohexane solution at 25°C.

^b ¹H-NMR measurements refer to trichloroethylene solution at -73 to -77°C.

The plot⁴⁴ of positions of conformational equilibria in 1,3-dialkylhexahydropyrimidines estimated by dipole-moment measurements against those estimated by J_{gem} measurements is improved by taking the J_{gem} of the diisopropyl derivative as -8.2^{292} rather than -10.0 Hz^{44}

The conformation **325** with the axial nitro group and both R groups equatorial has been shown to predominate for **325** (R = benzyl and R = cyclohexyl) by dipole-moment measurements^{293,294}, and J_{gem} values are in accord with this.²⁹⁵ For the related diethyl compound, a low-temperature (-63°C) ¹H-NMR spectrum shows **326** as the major conformer ($\Delta_{\text{ax,2eq}}$ 1.31 ppm) in equilibrium with **327** ($\Delta_{\text{ax,2eq}}$ 1.06 ppm).²⁹⁶

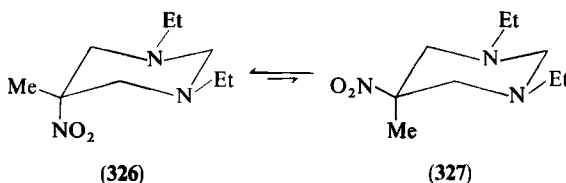


²⁹³ H. Piotrowska and T. Urbanski, *J. Chem. Soc.*, 1942 (1962).

²⁹⁴ D. Gurne, T. Urbanski, M. Witanowski, and L. Stefaniak, *Tetrahedron*, Suppl. 6, 195 (1964).

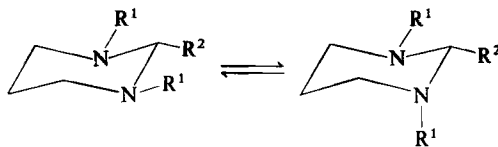
²⁹⁵ R. C. Cookson and T. A. Crabb, *Tetrahedron* 24, 2385 (1968).

²⁹⁶ T. Tsuji and Y. Okamoto, *Chem. Pharm. Bull. Jpn.* 20, 184 (1972).



The ring-inversion process in *N,N*-dimethylhexahydropyrimidine has been estimated by ^1H -NMR spectral studies as $\Delta G^\ddagger_{-31^\circ}$ 11.6 kcal mol $^{-1}$ ²⁹⁷ and $\Delta G^\ddagger_{-29 \pm 4^\circ}$ 11.3 kcal mol $^{-1}$ ²⁹⁸ Variable-temperature ^{13}C -NMR work²⁸⁷ permits the estimation of ΔG^\ddagger_c values (Table XXVII) for the N-inversion process in the *N,N*-dimethyl- and *N,N*-diethylhexahydropyrimidines.

TABLE XXVII
EQUILIBRIUM AND KINETIC PARAMETERS FOR THE N-INVERSION PROCESS
IN HEXAHYDROPYRIMIDINES²⁸⁷



Compound		ΔG_c° (kcal/mol $^{-1}$) ^a	ΔG_c^\ddagger (kcal mol $^{-1}$) ^a ee \rightarrow transition state	ΔG_c^\ddagger (kcal mol $^{-1}$) ^a ae \rightarrow transition state
R ¹	R ²			
Me	H	+0.7	7.6	6.9
Me	Me	-0.9	7.2	8.1
Et	H	+0.6	6.9	6.3
Et	Me	-0.4	6.7	7.1

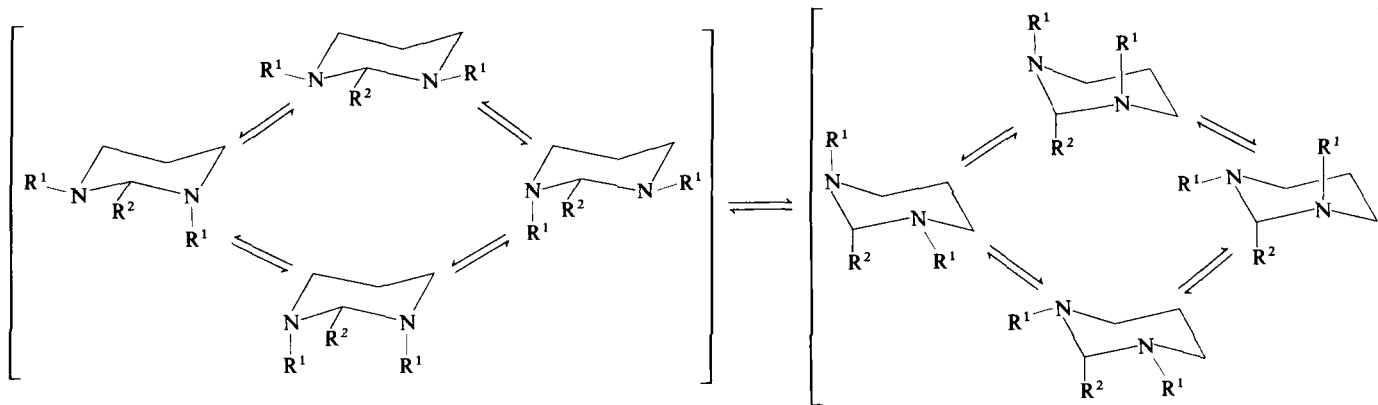
^a ΔG° and $\Delta G^\ddagger \pm 0.1$ kcal mol $^{-1}$, T_c -133 to -110°C.

c. *1,2,3-Trialkylhexahydropyrimidines*. A series of 2-alkyl-1,3-dimethylhexahydropyrimidines has been investigated by ^1H -NMR and by dipole moments.²⁷⁰ 1,2,3-Trimethyl- and 1,3-dimethyl-2-ethylhexahydropyrimidine have been investigated by ^1H -³⁰ and ^{13}C -NMR.²⁸⁷ The variable-temperature ^{13}C -NMR spectrum of 1,2,3-trimethylhexahydropyrimidine showed a first coalescence at -40°C for the ring-inversion process (C-methyl group conformational equilibrium) (Table XXVIII). The second coalescence for the N-inversion process occurred at -100°C. ^{13}C -NMR measurements at the first coalescence temperature gives ΔG^\ddagger 10.0 \pm 0.3 kcal

²⁹⁷ R. F. Farmer and J. Hamer, *Tetrahedron* **24**, 829 (1968).

²⁹⁸ F. G. Riddell, *J. Chem. Soc. B*, 560 (1967).

TABLE XXVIII
EQUILIBRIUM AND KINETIC PARAMETERS FOR THE RING INVERSION PROCESS IN HEXAHYDROPYRIMIDINES²⁸⁷



Compound		ΔG_c^\ddagger (kcal mol ⁻¹) ^{b,c}			
R ¹	R ²	ΔG_c° (kcal mol ⁻¹) ^{a,c}	C-2—R _{eq} conformers → transition state		C-2—R _{ax} conformers → transition state
Me	Me	+1.0	11.0	—	10.0
Et	Me	-0.4	9.4	—	9.8
<i>i</i> Pr	H	—	—	10.3	—

^a $\Delta G^\circ \pm 0.1$ kcal mol⁻¹.

^b $\Delta G_c^\ddagger \pm 0.3$ kcal mol⁻¹.

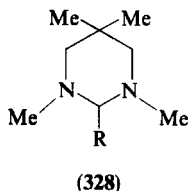
^c $T_c = 80^\circ$ to -40°C .

mol^{-1} for the C-methyl conformational equilibrium, which is shown by peak intensities to favor the equatorial C-Me by ΔG_c° 1.0 kcal mol^{-1} (Table XXVIII). Below the second coalescence, ΔG_c° is 0.9 kcal mol^{-1} in favor of the aee conformer. The substitution of the 2-equatorial H by 2-equatorial Me favors this aee conformer, both by lowering $\Delta G_{ee \rightarrow ts}^\ddagger$ and by raising $\Delta G_{ea \rightarrow ts}^\ddagger$ (Table XXVII).²⁸⁷

For 1,3-diethyl-2-methyl-1,3-hexahydropyrimidine, the ring inversion equilibrium favors the 2(ax)-Me conformer, and the data for the N-inversion equilibria (Table XXVII) refer to the set with 2(ax)-Me.²⁸⁷

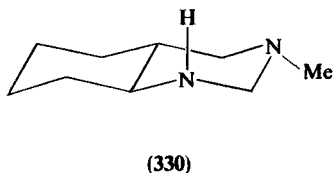
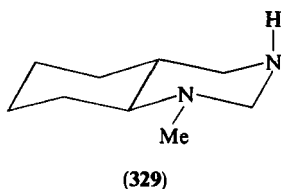
The ^1H -NMR spectrum shows that the aee conformer is favored also in the other 2-alkyl-1,3-dimethylhexahydropyrimidines.²⁷⁰

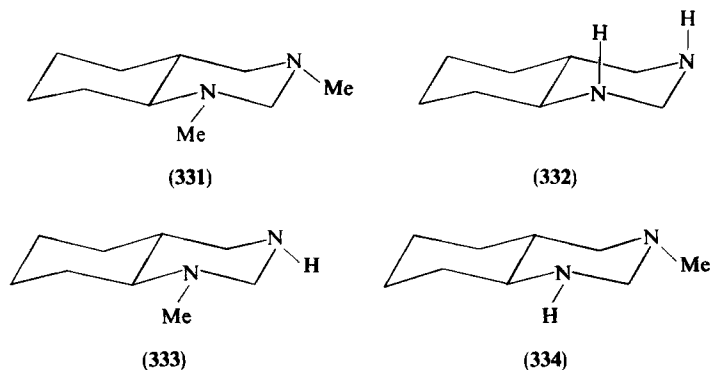
In the ^{13}C -NMR spectra of the 2-alkyl-1,3,5,5-tetramethylhexahydropyrimidines (328), the lower field absorption of the axial 5-methyl carbon in the 2-isopropyl and 2-*tert*-butyl derivatives than in 328 ($\text{R} = \text{Me}$ or $\text{R} = \text{Et}$) has been interpreted in terms of flexible nonchair conformations for 328 ($\text{R} = i\text{Pr}$ and *t*-Bu).⁹²



d. Bicyclic and Polycyclic Derivatives of Hexahydropyrimidine.

The conformational equilibria of *trans*-decahydroquinazoline and its *N*-methyl derivatives have been investigated. Comparison of J_{gem} values with those in locked or anancomeric systems (Table V) and with the value in 1-methylhexahydropyrimidine (319) was interpreted to demonstrate the existence of 329 and 330 in the depicted ae conformations and the 1,3-dimethyl derivative as $\sim 60\%$ ee 331 in equilibrium with ae conformers.⁶³ The J_{gem} of -12.6 Hz for *trans*-decahydroquinazoline itself was held to suggest predominantly the aa conformer 332 in the equilibrium. Later, dipole-moment measurements on these systems⁶² were interpreted to indicate that the 1-methyl derivative existed $\sim 60\%$ as ae 329 together with $\sim 40\%$ in the





conformation **333**, with both lone pairs axial. The 3-methyl compound was considered to exist $\sim 25\%$ in the *ae* conformation **330** and $\sim 75\%$ with both lone pairs axial (**334**).

It can no longer be claimed that dipole moments give reliable quantitative measures of conformational equilibria, and therefore the precise conformation of the perhydroquinazolines awaits low-temperature ^{13}C -NMR measurements. However, for the di-H-axial conformation **332** to be predominant would be unique: there is no evidence for any other hexahydropyrimidine existing even partially in such a conformation.

2-Methylperhydropyrido[1,2-*c*]pyrimidines may adopt the six all-chair conformations **335**–**340**, interconvertible by nitrogen inversion and/or ring inversion (Fig. 13). Conformers **338** and **339** are destabilized by three and four gauche-butane interactions, respectively, and conformer **340** by (among others) a 1,3-syn-diaxial interaction and, accordingly, these should make negligible contributions to the equilibrium. The unfavorable generalized anomeric effect present in the *trans* conformer **335** is relieved in the *trans* conformer **336** but at the expense of the introduction of a gauche-butane and gauche-propylamine interaction: **336** should contribute appreciably toward the equilibrium. In fact, dipole-moment measurements⁶¹ indicate $75\% \text{ } \mathbf{335} \rightleftharpoons 20\% \text{ } \mathbf{336} \rightleftharpoons 5\% \text{ } \mathbf{337}$, and this is confirmed by ^1H -NMR measurements.⁶⁵ Indications of the positions of conformational equilibria in a variety of methyl-substituted perhydropyrido[1,2-*c*]pyrimidines may be obtained from ^1H -NMR measurements. The conformational equilibrium for *cis*-(3-*H*,4*a*-*H*)-2,3-dimethylperhydropyrido[1,2-*c*]pyrimidine (**341**) resembles that for 2-methylperhydropyrido[1,2-*c*]pyrimidine (**335**–**341**), but the *trans*-(3-*H*,4*a*-*H*)-2,3-dimethyl derivative **342** \rightleftharpoons **343** adopts almost exclusively the axial *N*-methyl conformation **342**, *trans*-(4*a*-*H*,8-*H*)-2, 8-Dimethylperhydropyrido[1,2-*c*]pyrimidine **344** \rightleftharpoons **345** \rightleftharpoons **346** adopts an equilibrium containing ~ 40 – 50% of **344**.⁶⁵

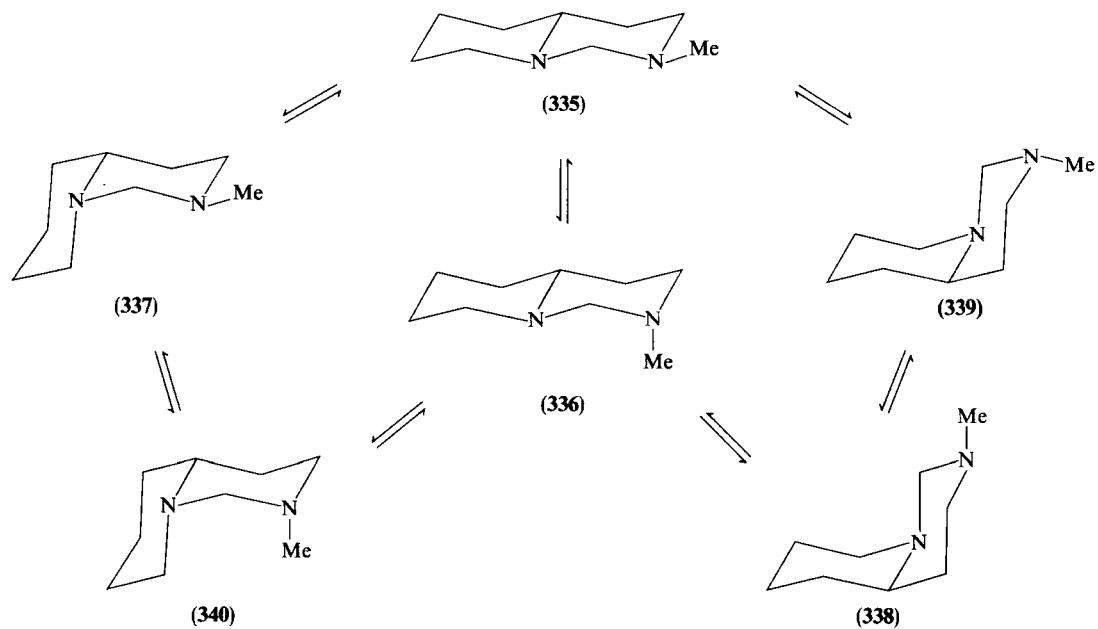
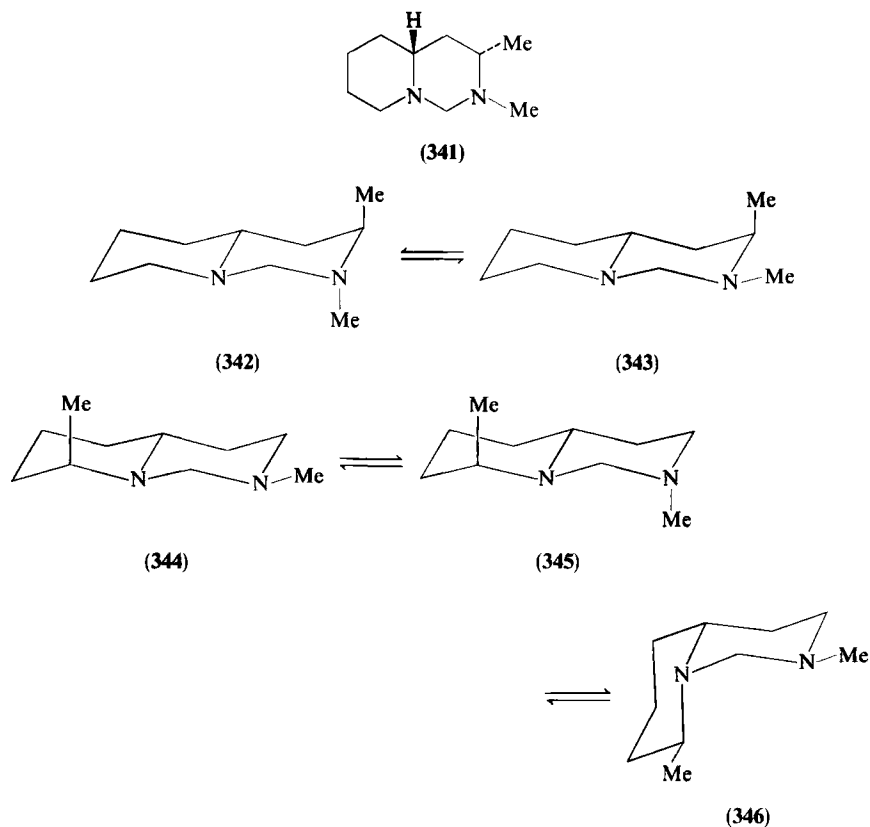
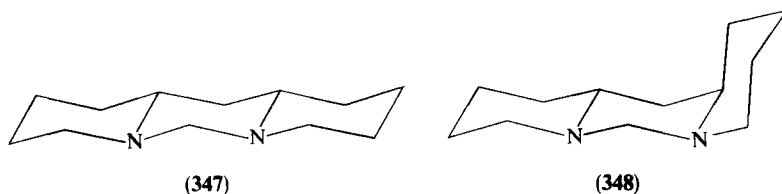
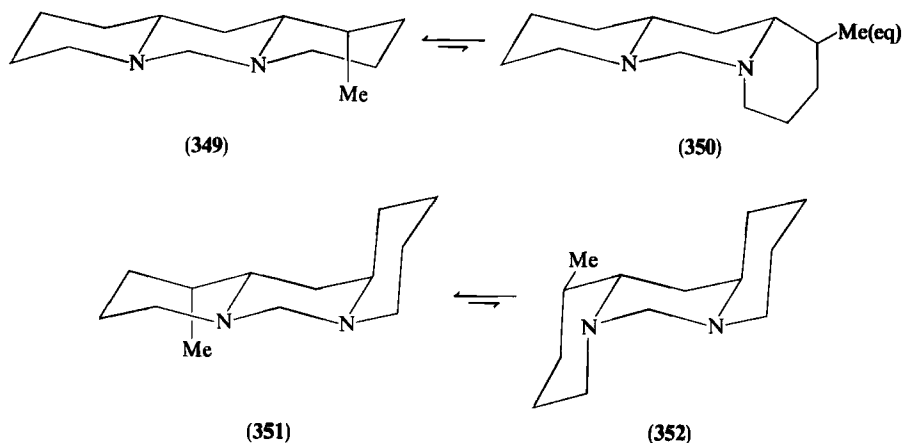


FIG. 13. Conformational equilibrium for 2-methylperhydropyrido[1,2-*c*]pyrimidine.



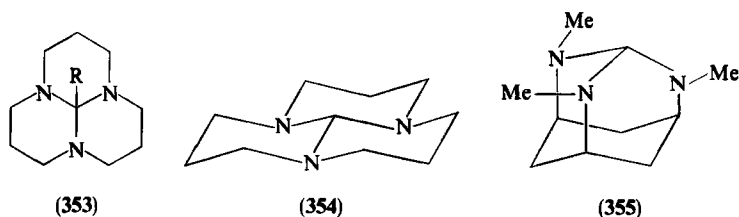
A ^1H -NMR study¹³⁷ of the conformational equilibria in *syn*- and *anti*-perhydrodipyrido[1,2-*c*;2',1'-*f*]pyrimidine indicates the existence of these exclusively in the conformations **347** and **348**. Substitution in **347** by axial methyl groups in the end rings shifts the equilibria somewhat toward the *cis*-fused conformation. Thus the *cis*-(1-*H*,12*a*-*H*)-1-methyl derivative adopts an equilibrium containing ~85% of the *trans*-*syn*-*trans* conformation **349** and ~15% of the *trans*-*syn*-*cis* conformation **350**. Similarly, the 1-methyl analog in the *anti* series exists as ~70% *trans*-*anti*-*cis* **351** with ~30% *cis*-*anti*-*cis* **352**.¹³⁷





The ^1H -NMR spectrum of the perhydro-3a,6a,9a-triazaphenalene **353** ($\text{R} = \text{H}$) shows absorption for the methine proton at δ 2.31, indicative of the trans-trans-trans conformation **354**.^{299,300} The shielding of the methine proton is shown by comparison³⁰⁰ with the absorption (δ 3.67) of the methine proton in **355**.³⁰¹ The ^{13}C -NMR spectrum of **353** ($\text{R} = \text{Me}$) at ambient temperatures shows a chemical shift of the methyl carbon at δ -6.6, consistent with the predominance of the trans-trans-trans conformation. It has been estimated that the equilibrium contains $\sim 14\%$ of the cis-cis-trans conformation **356**.³⁰²

The ^{13}C -NMR spectrum of the ethyl-substituted derivative at -80°C is consistent with the cis-cis-trans conformation and a complete line-shape analysis of the coalescence of the CH_2N resonances at higher temperatures gives ΔG^\ddagger 11.76 ± 0.2 kcal mol $^{-1}$ at -40°C for the inversion processes $\text{357} \rightleftharpoons \text{358} \rightleftharpoons \text{359}$.³⁰²

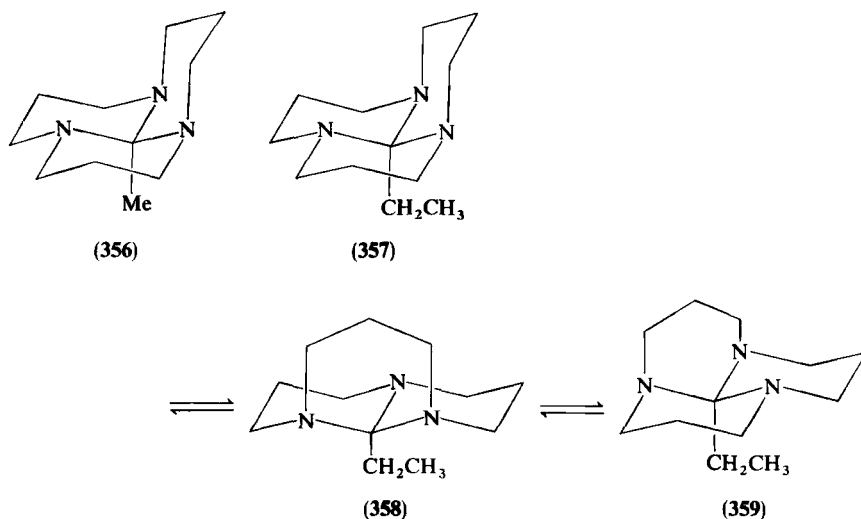


²⁹⁹ T. J. Atkins, *J. Am. Chem. Soc.* **102**, 6364 (1980).

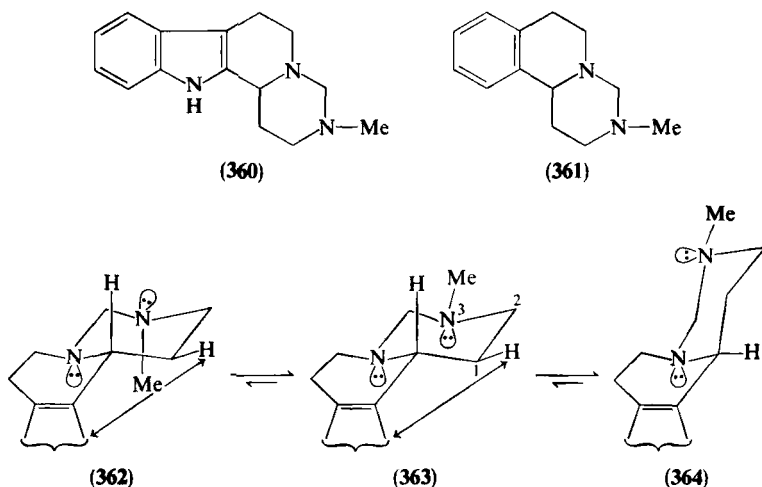
³⁰⁰ G. R. Weisman, V. Johnson, and R. E. Fiala, *Tetrahedron Lett.* **21**, 3635 (1980).

³⁰¹ H. Stetter and J. Bremen, *Chem. Ber.* **106**, 2523 (1973).

³⁰² G. R. Weisman, V. B. Johnson, and M. B. Coolidge, *Tetrahedron Lett.* **22**, 4365 (1981).

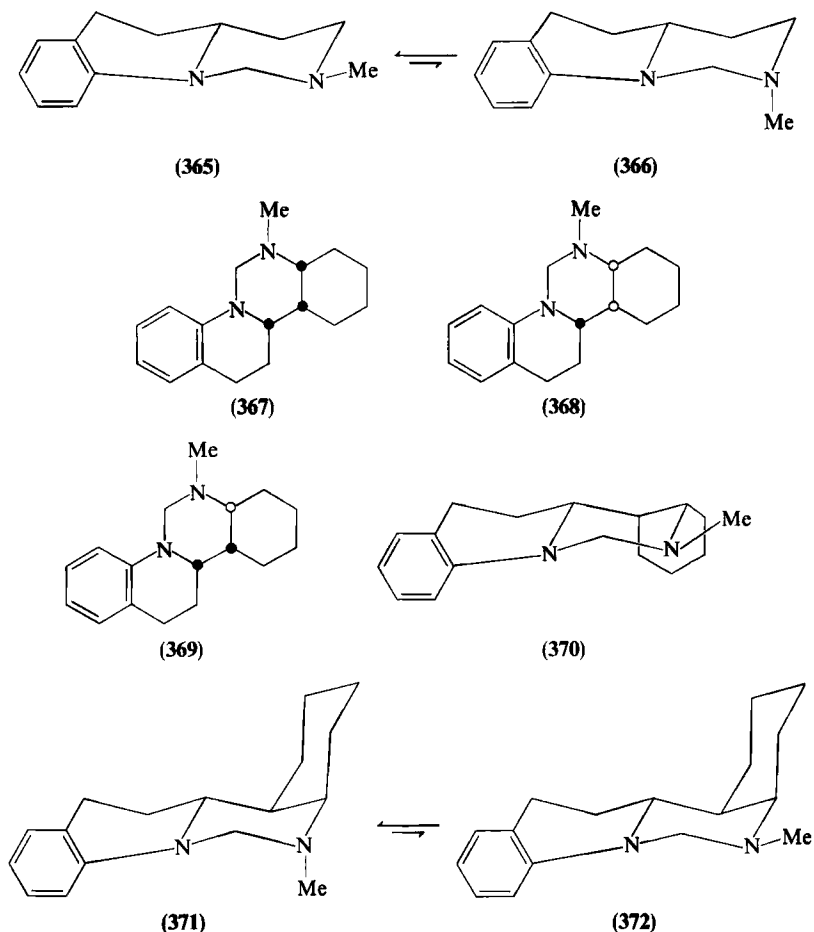


Indolo or benzo fusion at the 5,6-position in perhydropyrido[1,2-*c*]pyrimidine (335–340) (Fig. 13), as in **360** and **361** shifts the equilibrium in favor of the *cis*-fused conformer **364** and the axial *N*-methyl *trans*-fused conformer **362**, with ~54% of the equatorial *N*-methyl *trans*-fused conformer **363** present at room temperature (CDCl_3 solution).^{284,285} The shift in equilibrium (compare corresponding shift for **192–194** compared to quinolizidine **179–181**, Section III,B,3) is presumably a result of a destabilization of **362** and **363** by the peri-type interaction involving the C-1-H and either the

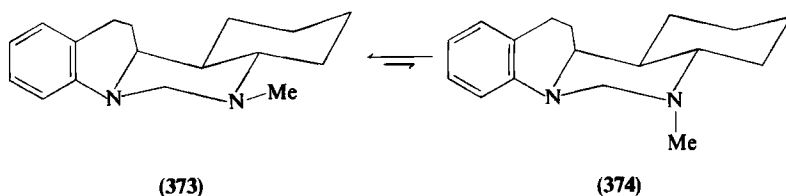


indole *N*-H or the aryl *C*-11-H in **361** and a destabilization arising from parallel *N*-3 lone pair and aromatic ring orbitals.

In contrast, the 7,8-benzo-fused perhydropyridol[1,2-*c*]pyrimidine 2-methyl-2,3,4,4*a*,5,6-hexahydro-1*H*-pyrimido[3,4-*a*]quinoline exists in solution as ~80% equatorial *N*-methyl trans conformer **365** in equilibrium with ~20% of the axial *N*-methyl trans conformer **366**.³⁰³ ¹H-NMR studies³⁰³ on three diastereoisomeric 7-methyl-6,7,8,9,10,11,11*a*,11*b*,12,13-decahydro-7*aH*-quino[1,2-*c*]quinazolines **367**–**369** indicate the almost exclusive existence of **367** in the trans-fused conformation **370**, of **368** as ~56% **371** ⇌ 44% **372** and of **369** as ~80% **373** ⇌ 20% **374**. The conformational preferences



³⁰³ T. A. Crabb and J. S. Mitchell, *J. C. S. Perkin II*, 581 (1979).



for **368** and **369** may be explained in terms of difference in nonbonded interactions. Thus the unfavorable generalized anomeric effect present in **372** may be relieved in **371** at the expense of the introduction of only a gauche-propylamine-type interaction and, accordingly, **371** will be favored. In **374** the unfavourable anomeric effect present in **373** is relieved only at the expense of the introduction of a gauche-pyropylamine and a gauche-butane interaction, and so the equilibrium favors **373**.³⁰³ Dynamic changes in the ^{13}C -NMR spectrum of *cis*-1,3,4,7,8-pentamethyl-1,3,7-triazabicyclo[3.3.1]nonane at temperatures below -90°C have been interpreted²⁸⁹ as a slowing of the $375 \rightleftharpoons 376$ and $377 \rightleftharpoons 378$ processes with the nitrogen inversion $375 \rightleftharpoons 377$ remaining fast (Fig. 14). Application of the Anet equations

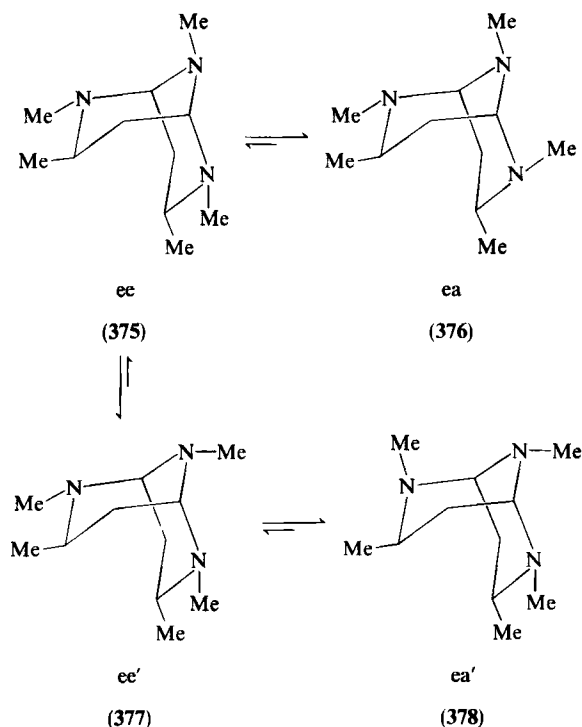
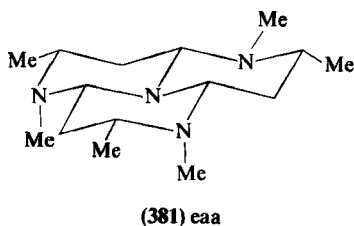
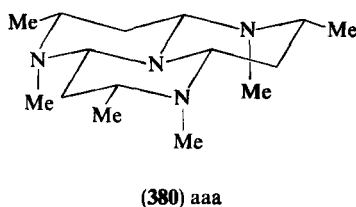
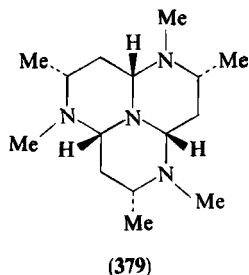


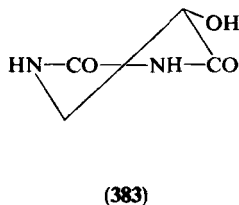
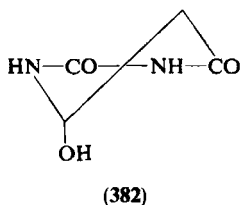
FIG. 14. Part of conformational equilibrium for *cis*-1,3,4,7,8-pentamethyl-1,3,7-triazabicyclo[3.3.1]nonane.

(Section II,B,5) gave $\Delta G_{ax \rightarrow eq}^\ddagger$ 7.3 ± 0.2 kcal mol⁻¹ (at -105°C) and ΔG_{-105}° 0.96 ± 0.05 kcal mol⁻¹, favoring the **375** conformer.

Similar studies²⁸⁹ on the perhydro-1,2,4,5,6,8-hexamethyl-1,4,7,9b-tetraazaphenalene **379** gave for the $380 \rightleftharpoons 381$ equilibrium $\Delta G_{caa \rightarrow aaa}^\ddagger$ 8.0 ± 0.2 kcal mol⁻¹ at -105°C and ΔG_{-105}° 0.4 ± 0.1 kcal mol⁻¹, favoring the aaa conformer **380**.



e. *Perhydropyrimidinones*. IR and ¹H-NMR³⁰⁴ spectral studies on derivatives of dihydrouracil and dihydrothymidine show the differing conformational preferences for a C-5- as opposed to a C-6-hydroxy substituent. Thus in the half-chair conformation, the C-6-OH group prefers the axial orientation (60%) **382** and the C-5-OH the equatorial orientation (95%) **383**. In contrast, the C-5-Br group prefers the axial orientation.³⁰⁴

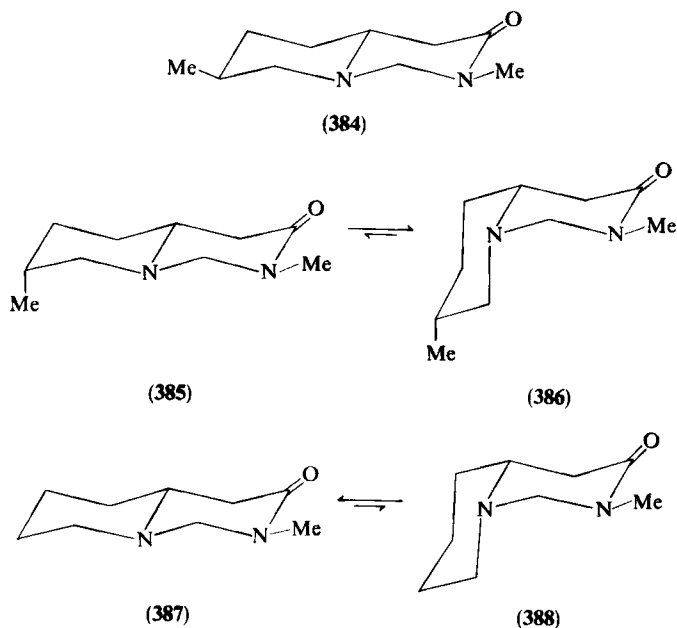


The ¹H-NMR and IR (Bohlmann region, Section II,E,1) spectra of perhydropyrido[1,2-*c*]pyrimidin-3-ones suggest³⁰⁵ the existence of the *trans*-(4a-

³⁰⁴ C. Nofre, M. Murat and A. Cier, *Bull. Soc. Chim. Fr.*, 1749 (1965); M. Chabre, D. Gagnaire, and C. Nofre, *ibid.*, 108 (1966).

³⁰⁵ T. A. Crabb and R. F. Newton, *J. C. S. Perkin II*, 1920 (1972).

H,7-*H*)-2,7-dimethyl derivative exclusively in the trans conformation **384**, of the *cis*-(4*a*-*H*,7-*H*)-2,7-dimethyl derivative as an equilibrium **385** \rightleftharpoons **386** favoring the *cis*-fused conformation ($\sim 70\%$) **386** and of the parent compound as **387** \rightleftharpoons **388** with $\sim 84\%$ trans-fused conformation. The *cis*-fused analog **337** (Fig. 13) of **338** is present to a smaller extent in the 2-methylperhydropyrido[1,2-*c*] pyrimidine equilibrium.



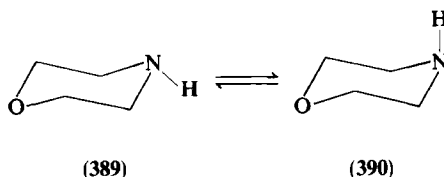
E. 1,4-HETEROCYCLIC SYSTEMS

1. Morpholines

a. *Monocyclic Systems.* The low-temperature $^1\text{H-NMR}$ spectrum of morpholine³⁰⁶ and the *R* value^{70,71} (Table VI) are consistent with the chair conformation.³⁰⁶ From a temperature study of the IR spectrum of morpholine in the first *N-H* overtone region, ΔH° of $0.5 \pm 0.1 \text{ kcal mol}^{-1}$ (in the gas phase) has been deduced¹⁴¹ for the equilibrium **389** \rightleftharpoons **390**, a value close to that for piperidine. For morpholine in carbon tetrachloride solution, a value for ΔH° of $0.6 \pm 0.1 \text{ kcal mol}^{-1}$ has been estimated.¹⁴¹ The microwave spectrum of morpholine shows the predominance of lines for the *N-H*_{eq}

³⁰⁶ R. A. Spragg, *J. Chem. Soc. B*, 1128 (1968).

conformer³⁰⁷ and this is in accord with a theoretical conformational analysis of morpholine.³⁰⁸ Very early dipole-moment and Kerr-constant measurements³⁰⁹ were taken to indicate 37% *N*-H_{eq} conformer **389** in cyclohexane and 13% **389** in benzene, but these results can no longer be considered reliable.



By analogy with the results on *N*-methylpiperidine, it is to be expected that the *N*-Me_{eq} conformer of *N*-methylmorpholine will be strongly favored. Early dipole-moment measurements³⁰⁹ gave ΔG_{25}° 0.17 kcal mol⁻¹ (cyclohexane), but this must be far too low. The microwave spectrum corresponds to the chair form with the equatorial *N*-methyl group³¹⁰ and the magnitudes of the *N*-Me substituent γ - and β -effects (Section II,B,5) at C-2 (C-6) (−1.0 ppm) and at C-3 (C-5) (9 ppm) are similar to those in *N*-methylpiperidine and indicate a conformational equilibrium strongly in favor of *N*-Me equatorial.³¹¹ Attempts³¹² to apply the *N*-methyl group line-broadening method to the elucidation of the conformational equilibrium of *N*-methylmorpholine failed.³¹³

¹H-NMR studies on 2,6-dimethylmorpholine³¹⁴ and *N*-substituted 2,6-dimethylmorpholines³¹⁵ are consistent with the single diequatorial conformation **391** for the *cis* isomers and with the equilibrium **392** \rightleftharpoons **393** for the *trans* isomers. The ¹³C-NMR spectrum of the monomethyl-, 2,3-, 2,5-, 2,6-, 3,5-dimethyl-, 2,3,4-, 2,3,6-trimethyl-, and 2,3,5,6-tetramethylmorpholines are largely consonant with expectations based on conformational principles derived from cyclohexane conformational analysis.³¹⁶ The all-*cis* 2,3,5,6-isomer, which did not prove amenable to analysis by ¹H-NMR spectro-

³⁰⁷ J. J. Sloan and R. Kewley, *Can. J. Chem.* **47**, 3453 (1969).

³⁰⁸ A. L. Capparelli, J. Marañón, O. M. Sorarrain, and R. R. Filgueira, *J. Mol. Struct.* **23**, 145 (1974).

³⁰⁹ M. J. Aroney, C.-Y. Chen, R. J. W. LeFèvre, and J. D. Saxby, *J. Chem. Soc.*, 4269 (1964).

³¹⁰ S. C. Dass and R. Kewley, *Can. J. Chem.* **52**, 434 (1974).

³¹¹ A. J. Jones, C. P. Beeman, M. U. Hasan, A. F. Casy, and M. M. A. Hassan, *Can. J. Chem.* **54**, 126 (1976).

³¹² V. J. Baker, I. J. Ferguson, A. R. Katritzky, and R. Patel, *Tetrahedron Lett.*, 4735 (1976).

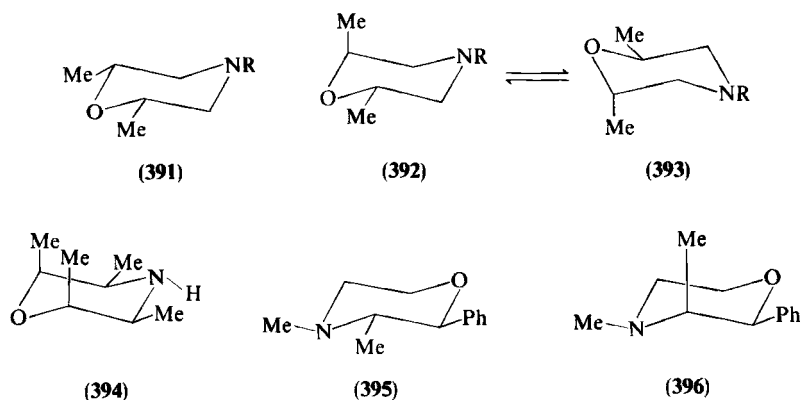
³¹³ A. R. Katritzky, R. C. Patel, and D. M. Read, *Tetrahedron Lett.*, 3803 (1977).

³¹⁴ H. Booth and G. C. Gidley, *Tetrahedron* **21**, 3429 (1965).

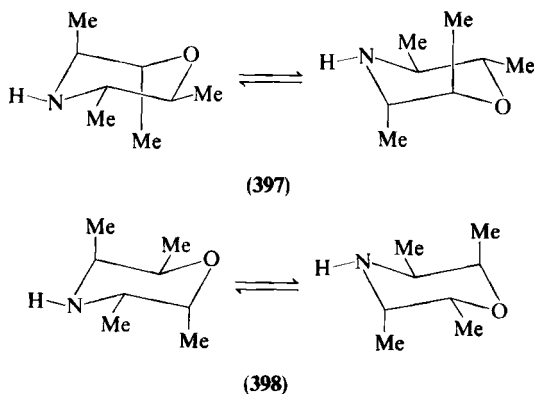
³¹⁵ W. Brügel, *Org. Magn. Reson.* **1**, 425 (1969).

³¹⁶ B. Nilsson and S. Hernestam, *Org. Magn. Reson.* **11**, 116 (1978).

scopy,³¹⁷ appears to adopt the conformation **394**. Both isomers of 3,4-dimethyl-2-phenylmorpholine have been studied by ¹H-NMR³¹⁸ and by ¹³C-NMR spectroscopy³¹¹ and shown to adopt the conformations **395** and **396**.



Ring-inversion barriers for the 2,3,5,6-tetramethylmorpholines **397** and **398** (ΔG^\ddagger 8.0 kcal mol⁻¹ at -107°C and ΔG^\ddagger 10.55 kcal mol⁻¹ at -75°C)³¹⁷ bracket the value of ΔG^\ddagger 9.80 kcal mol⁻¹ (-70°C) determined on 2,2,6,6- and 3,3,5,5-tetradeuteromorpholine. The ΔG^\ddagger value of 11.5 kcal mol⁻¹ (-31°C) for ring inversion in *N*-methylmorpholine³²⁰ is similar to that in *N*-methylpiperidine.



³¹⁷ S. Hernestam and B. Nilsson, *Org. Magn. Reson.* **8**, 582 (1976).

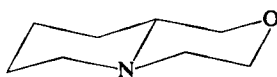
³¹⁸ D. Dvornik and G. Schilling, *J. Med. Chem.* **8**, 466 (1965).

³¹⁹ P. Le Cam and J. Sandström, *Chem. Scr.* **1**, 65 (1971).

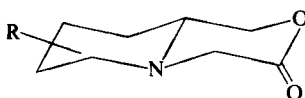
The conformational free energy (0.99 ± 0.02 kcal mol⁻¹ at -70°C) of the *N*-chloro group in *N*-chloro-2,6-dimethylmorpholine¹⁷⁷ is slightly less than that in *N*-chloro-2,6-dimethylpiperidine (Section III,A,1,c).

Half-chair conformations are indicated for a range of substituted morpholin-2-ones.^{321,322}

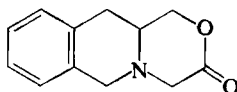
b. *Bi- and Tricyclic Derivatives.* The *trans*-fused conformation **399** is strongly favored for perhydropyrido[2,1-*c*][1,4]oxazine⁶⁷ and for an extensive range of reduced and partially reduced pyrido[2,1-*c*][1,4]oxazin-3-ones **400–402**.³²³ The related [1,4]oxazin-4-ones **403** and **404** adopt conformations such that the 4-keto group bisects the C-3 methylene,³²⁴ and *cis*-(6-*H*, 9*a-H*)-6-methylperhydropyrido[1,4]oxazin-4-one exists in a twist-chair ring-A confirmation **405**.³²⁴ The *trans*-BC ring fusion is adopted by r-9,t-13,c-14-8-aza-12-oxa-1,3,4-estratriene.^{324a}



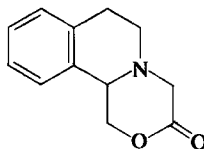
(399)



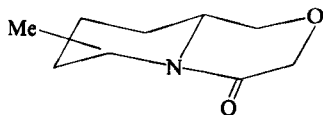
(400)



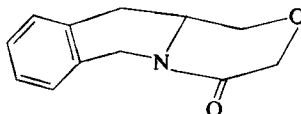
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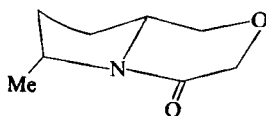
(402)



(403)



(404)



(405)

³²⁰ R. K. Harris and R. A. Spragg, *Chem. Commun.*, 314 (1966).

³²¹ R. Cahill and T. A. Crabb, *Tetrahedron* **25**, 1513 (1969).

³²² S. L. Spassov, J. N. Stefanovsky, B. J. Kurtev, and G. Fodor, *Chem. Ber.* **105**, 2467 (1972).

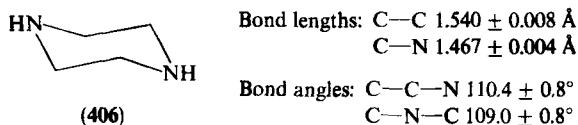
³²³ R. Cahill and T. A. Crabb, *Org. Magn. Reson.* **4**, 509 (1972).

³²⁴ R. Cahill and T. A. Crabb, *Org. Magn. Reson.* **4**, 283 (1972).

^{324a} G. Bernáth, F. Fülöp, G. Argay, A. Kálmán, and P. Sohár, *Tetrahedron Lett.* **22**, 3797 (1981).

2. Piperazines

a. *Monocyclic Systems.* The R value^{70,71} (Table VI, Section II,B,3) of 2.15 for piperazine (**406**) is consistent with the chair conformation demonstrated by electron-diffraction measurements.³²⁵ IR N -H overtone measurements²³⁶ on *N*-*tert*-butylpiperazine show the predominance of N -H_{eq} and dipole-moment measurements give 63% N -H_{eq} (cyclohexane solution at 25°C).²³⁶



Dipole-moment measurements in benzene solution on 1,4-dimethylpiperazine and on a series of 1-alkyl-4-*tert*-butylpiperazines¹²⁰ show clearly that the N -alkyl groups exist predominantly in the expected position and indicate a value of ~ 1.8 kcal mol⁻¹ for the N -methyl group. This must now be considered a minimum value, and kinetic protonation of 1,4-dimethylpiperazine with ¹³C-NMR analysis of the products³²⁶ gives 2.96 ± 0.05 kcal mol⁻¹. An attempt³¹² to apply the line-broadening method failed.³¹³

Dielectrometric titration in dioxane against *tert*-butylbenzenesulfonic acid³²⁷ and ultrasonic measurement (Section II,I) (ΔH° 1.3 kcal mol⁻¹) also gives low estimates. X-Ray results³²⁸ on *N,N*-dimethylpiperazine show a flatter chair than in cyclohexane, with both N -methyl groups equatorial. Barriers to ring inversion have been estimated as ΔG^\ddagger 10.3 kcal mol⁻¹ for piperazine, 11.5 kcal mol⁻¹ for *N*-methylpiperazine,³²⁹ and 13.6 kcal mol⁻¹ (25°C in CCl₄) for *N,N*-dimethylpiperazine.³³⁰ A distinction between the *cis* and *trans* isomers of 2,3-, 2,5-, and 2,6-dimethylpiperazines was made on the basis of changes in the ¹H-NMR spectra in the temperature range 0 to -80°C, with the spectra of the *ae*-dimethyl isomers (*ae* \rightleftharpoons *ea* equilibria) showing broadening at low temperatures.³³¹

At -45°C the ¹³C-NMR spectrum of *N,N*-dichloropiperazine shows absorption for the *ee* and *ea* conformers, giving ΔG° 0.5 kcal mol⁻¹ (-45°C) favoring the diequatorial conformer **407**.³³² This represents a much reduced

³²⁵ A. Yokozeki and K. Kuchitsu, *Bull. Chem. Soc. Jpn.* **44**, 2352 (1971).

³²⁶ F. A. L. Anet and I. Yavari, *Tetrahedron Lett.*, 2093 (1976).

³²⁷ I. Horikoshi, M. Morü, and N. Takeguchi, *Chem. Pharm. Bull.* **23**, 754 (1975).

³²⁸ M. Davis and O. Hassel, *Acta Chem. Scand.* **17**, 1181 (1963).

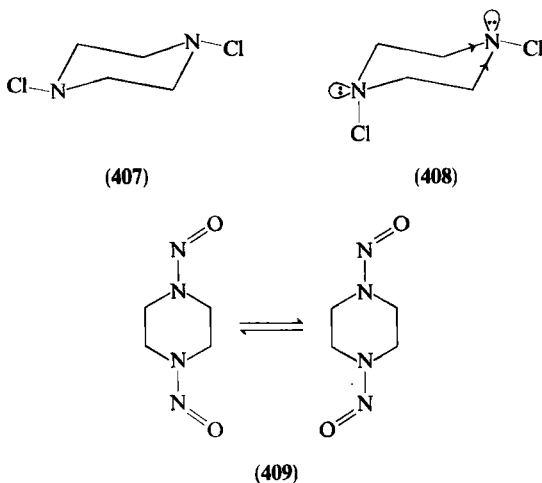
³²⁹ R. K. Harris and R. A. Spragg, *J. Chem. Soc. B*, 684 (1968).

³³⁰ R. G. Lett, L. Petrakis, A. F. Ellis, and R. K. Jensen, *J. Phys. Chem.* **74**, 2816 (1970).

³³¹ M. Tsutsui, T. Watanabe, and A. Ohta, *J. Heterocycl. Chem.* **17**, 809 (1980).

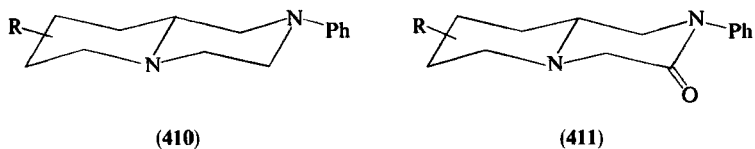
³³² F. A. L. Anet and I. Yavari, *Chem. Commun.*, 58 (1978).

preference for $N\text{-Cl}_{\text{eq}}$ than in $N\text{-chloropiperidine}$ ($\Delta G^\circ 1.5 \pm 0.1 \text{ kcal mol}^{-1}$ at -98°C , favoring $N\text{-Cl}_{\text{eq}}$, Section III,A,1), and this has been interpreted in terms of a possible stabilization of the *ae* form **408** by the generalized anomeric effect in which the $\text{CH}_2\text{---N}(\text{Cl}_{\text{eq}})\text{---CH}_2$ system reduces the electron density in the C---C bonds anti-coplanar with the equatorial nitrogen lone pair.³³²

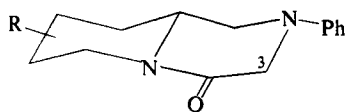


N,N -Dinitrosopiperazine (**409**) exists in CH_2Cl_2 solution at 40°C as a mixture of the syn and anti forms in which the anti form predominates. The R value (1.5) of the anti form indicates its adoption of a boat form or a very flattened chair.³³³

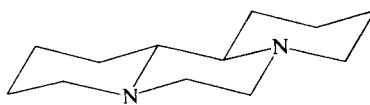
b. Bi- and Tricyclic Derivatives. 2-Phenylperhydropyrido[1,2-*a*]pyrazines and some ring-A methyl-substituted derivatives strongly favor the trans-fused conformation **410**, this preference being shared by the 3-oxo derivatives **411**. The 4-oxo derivatives adopt a conformation (**412**) such that the C=O group bisects the C-3 methylene.⁶⁷ The *anti*- and *syn*-perhydrodipyrido[1,2-*a*:2',1'-*c*]pyrazines adopt exclusively the conformations **413** and **414** (weaker Bohlmann bands in **414** than in **413**, Section II,E,1), and the



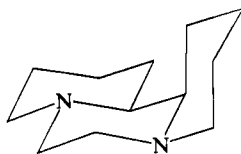
³³³ J. B. Lambert, J. L. Gosnell, Jr., D. S. Bailey, and B. M. Henkin, *J. Org. Chem.* **34**, 4147 (1969).



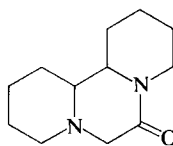
(412)



(413)



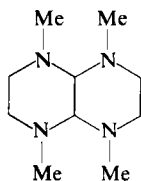
(414)



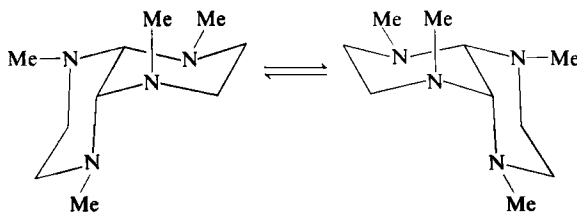
(415)

marked Bohlmann bands in both the corresponding 6-oxo derivatives **415** also indicate the A-B transfusion.³³⁴

Neglecting high energy conformations, *cis*-1,4,5,8-tetramethylperhydro[2,3-*b*]pyrazinopyrazine (**416**) exists as an enantiomeric pair of conformers **417** and **418** interconverting by ring inversion. For the *trans* isomer, only conformations **419** and **420** need to be considered. A ¹³C- and ¹H-NMR

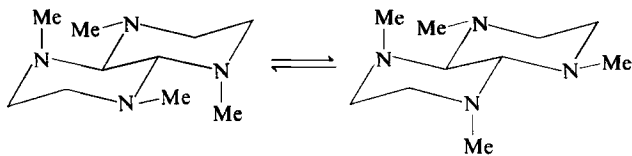


(416)



(417)

(418)

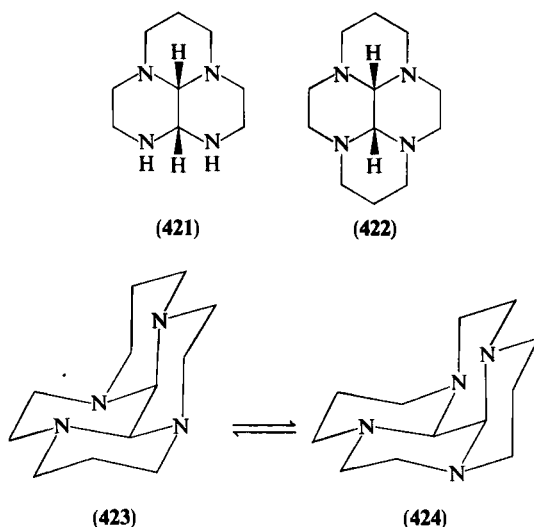


(419)

(420)

³³⁴ P. J. Chivers, T. A. Crabb, and R. O. Williams, *Tetrahedron* **24**, 4411 (1968).

study of a mixture of the *cis* and *trans* isomers uncovers two processes, at -74°C the slowing of the $\text{cis} \rightleftharpoons \text{cis}$ interconversion (ΔG^{\ddagger} $11.6 \text{ kcal mol}^{-1}$) and at -109°C the slowing of nitrogen inversion in the *trans* isomer (ΔG^{\ddagger} $9.1 \text{ kcal mol}^{-1}$).³³⁵ These conclusions have recently been confirmed, and the structure of the *trans* compound ($419 \rightleftharpoons 420$), was anchored by X-ray investigation.³³⁶ Tricyclic (421)³³⁷ and tetracyclic (422)^{338,339} analogs have also been studied. $\Delta G_{\text{e}}^{\ddagger}$ of $15.57 \pm 0.2 \text{ kcal mol}^{-1}$ at 47°C in CDCl_3 has been determined³³⁹ for the inversion process $423 \rightleftharpoons 424$.



F. 1,2,4-HETEROCYCLIC SYSTEMS

1. Tetrahydro-1,4,2-dioxazines

The conformational equilibria for tetrahydro-1,4,2-dioxazines (425) should combine the characteristic features of the equilibria for tetrahydro-1,3-oxazines (Section III,D,1) and tetrahydro-1,2-oxazines (Section III,C,1). Thus by analogy with the 3-methyltetrahydro-1,3-oxazine equilibrium (ΔG° $N\text{-Me}_{\text{eq}} \rightleftharpoons N\text{-Me}_{\text{ax}} -0.10 \pm 0.05 \text{ kcal mol}^{-1}$ at -120°C , Table XX), in the

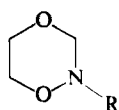
³³⁵ I. J. Ferguson, A. R. Katritzky, and R. Patel, *J. C. S. Perkin II*, 1564 (1976).

³³⁶ B. Fuchs, S. Weinman, U. Shmueli, A. R. Katritzky, and R. C. Patel, *Tetrahedron Lett.* **22**, 3541 (1981).

³³⁷ J. Jazwinski and R. A. Kolinski, *Tetrahedron Lett.* **22**, 1711 (1981).

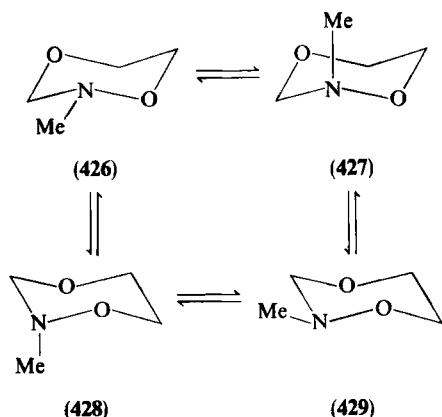
³³⁸ R. A. Kolinski and F. G. Riddell, *Tetrahedron Lett.* **22**, 2217 (1981).

³³⁹ G. R. Weisman, S. C. H. Ho, and V. Johnson, *Tetrahedron Lett.* **21**, 335 (1980).



(425)

equilibrium of Fig. 15, conformers **427** and **428** should be favored as a consequence of the generalized anomeric effect and the reduced (relative to tetrahydro-1,2-oxazine) syn-axial interaction involving the axial *N*-Me group and O-4. However, by analogy with 2-methyltetrahydro-1,2-oxazine ($\Delta G^\circ N\text{-Me}_{\text{eq}} \rightleftharpoons N\text{-Me}_{\text{ax}} \geq 2.0 \text{ kcal mol}^{-1}$ Section III,C,1, but see below) **426** and **429** should be favored. Low-temperature $^1\text{H-NMR}$ spectra of 2-methyl-1,4,2-dioxazine (**425**; $\text{R} = \text{Me}$) permitted identification of both types of conformer (**426**, $J_{\text{gem}} -9.2 \text{ Hz}$; **429**, $J_{\text{gem}} -10.2 \text{ Hz}$) and gave $\Delta G^\circ_{-82^\circ} 1.03 \text{ kcal mol}^{-1}$ for the $N\text{-Me}_{\text{eq}} \rightleftharpoons N\text{-Me}_{\text{ax}}$ equilibrium—a value indeed intermediate between the values for the 1,3- and 1,2-oxazines.³⁴⁰

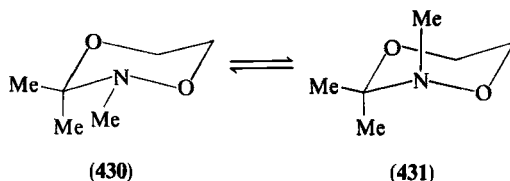
FIG. 15. Conformational equilibrium for *N*-methyltetrahydro-1,4,2-dioxazine.

Comparison of the conformational free energies for the *N*-methyl group in *N*-methylpiperidine ($2.7 \text{ kcal mol}^{-1}$) and in *N*-methyltetrahydro-1,3-oxazine ($\Delta G^\circ \sim 0 \text{ kcal mol}^{-1}$) with the value of $1.0 \text{ kcal mol}^{-1}$ for the 1,4,2-dioxazine just mentioned, suggests that the corresponding free energy of the methyl group in *N*-methyltetrahydro-1,2-oxazine may be nearer $2.7 + 1.0 = 3.7 \text{ kcal mol}^{-1}$.

2-Ethyltetrahydro-1,4,2-dioxazine (**425**; $\text{R} = \text{Et}$) showed an increased preference for the axial *N*-Et conformation ($\Delta G^\circ_{-82^\circ} 0.72 \text{ kcal mol}^{-1}$) (compare

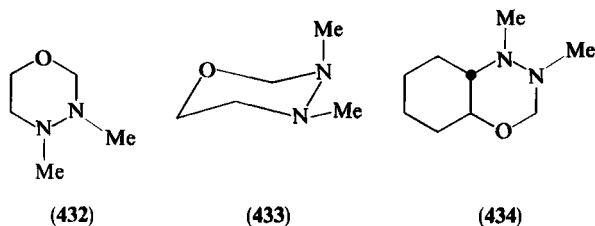
³⁴⁰ R. A. Y. Jones, A. R. Katritzky, A. R. Martin, and S. Saba, *Chem. Commun.*, 908 (1973); *J. C. S. Perkin II*, 1561 (1974).

N-methyl- and *N*-ethyltetrahydro-1,3-oxazine in Table XXI).³⁴⁰ The 6-ethyl group also shows a greater axial preference than 6-methyl.³⁴¹ In addition, in line with expectations based on similarly substituted 1,3-heterocyclic systems (Section III,D) the ΔG°_{-82} of 0.61 kcal mol⁻¹ for 2,3,3-trimethyltetrahydro-1,4,2-dioxazine (**430** \rightleftharpoons **431**) showed an increase in the *N*-Me_{ax} conformation relative to **426** (R = Me).³⁴⁰ Two inversion processes characterized by ΔG^\ddagger 11.7 \pm 0.2 kcal mol⁻¹ (-33.5°C) and ΔG^\ddagger 10.2 \pm 0.2 kcal mol⁻¹ (-64°C)³⁴⁰ were identified as nitrogen inversion (*N*-Me_{ax} \rightarrow transition state) and ring inversion, respectively, from a study of 2-methyl-6-alkyltetrahydro-1,4,2-dioxazines.³⁴¹



2. Tetrahydro-1,3,4-oxadiazines

The conformational equilibria for 3,4-dimethyltetrahydro-1,3,4-oxadiazines (**432**) (Fig. 16) should reflect the equilibria for *N*-methyltetrahydro-1,3-oxazine (ΔG° *N*-Me_{eq} \rightleftharpoons *N*-Me_{ax} -0.10 \pm 0.05 at -120°C, Table XXI) and for *N,N*-dimethylhexahydropyridazine (ΔG° *N*-Me_{eq} \rightleftharpoons *N*-Me_{ax} +0.22 kcal mol⁻¹ at -25°C).³⁴² Thus **432** should prefer the axial N-3 Me conformation (**433**) because here the 1,3-heterocyclic segment is favored by the generalized anomeric effect and the hydrazine segment by the preferred gauche lone-pair orientation. The analogy with the *N,N*-dimethyltetrahydropyridazine extends into the energetics of the inversion processes because there will be slow inversions involving passing of the two *N*-methyl groups crossing vertical line in Fig. 16) and faster nonpassing inversions—the eight



³⁴¹ F. G. Riddell, M. H. Berry, and E. S. Turner, *Tetrahedron* **34**, 1415 (1978).

³⁴² I. J. Ferguson, A. R. Katritzky, and D. M. Read, *J. C. S. Perkin II*, 1861 (1976).

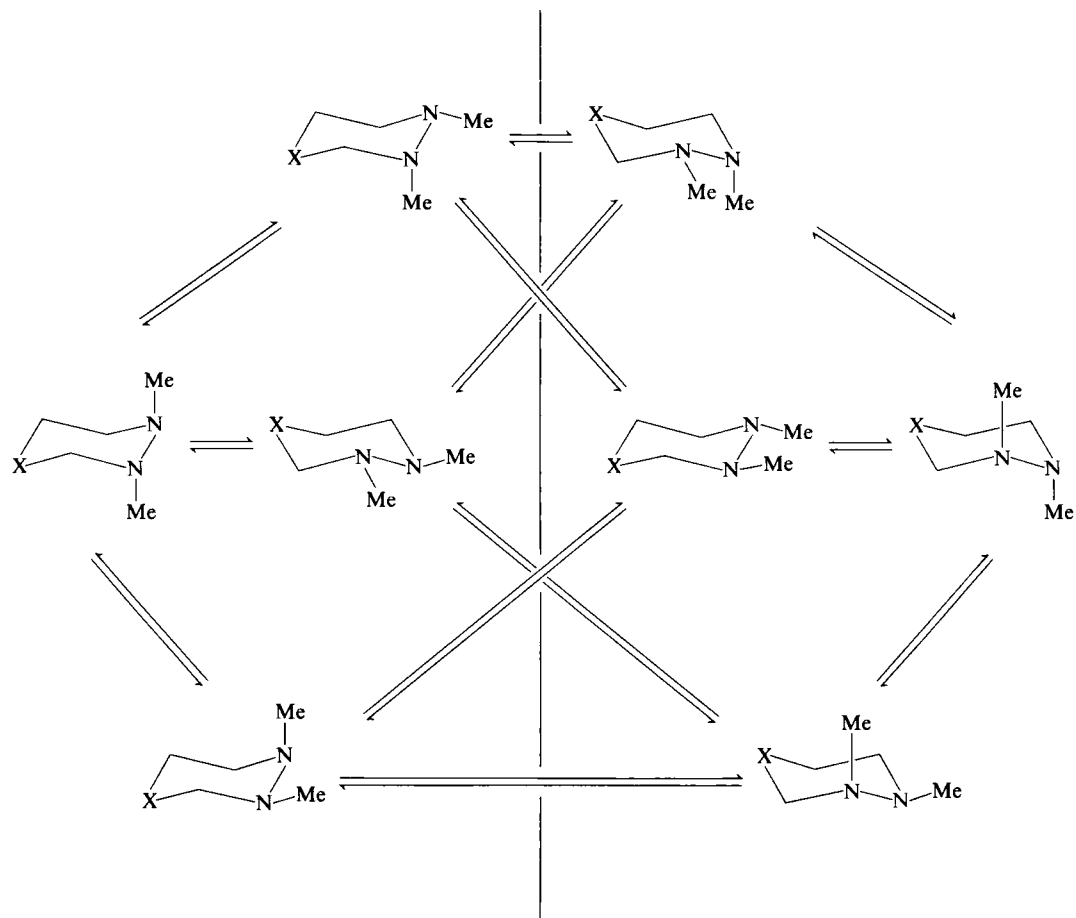


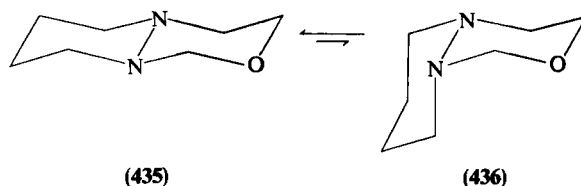
FIG. 16. Conformational equilibrium in *N,N*-dimethyltetrahydro-1,3,4-oxadiazine ($X = O$),³⁵⁰ *N*-methyltetrahydro-1,3,4-thiadiazine ($X = S$),³⁴⁹ and 1,2,4-trimethylhexahydro-1,2,4-triazine ($X = NMe$).⁹⁶

possible conformations in Fig. 16 being split by the vertical line into two enantiomeric sets.

The low temperature ^1H -NMR spectrum^{342,343} shows **433** to be the major conformer ($J_{\text{gem}} -10.1$ Hz at 80°C ; see Table V for locked derivative), and ΔG°_{-23} is estimated³⁴³ as >1.5 kcal mol $^{-1}$ ($\text{ae} \rightleftharpoons \text{ee}$). The slow process ΔG^\ddagger 12.6 ± 0.2 kcal mol $^{-1}$ at $\sim -23^\circ\text{C}$ ³⁴² was first assigned to a nonpassing ring inversion³⁴² (ΔH^\ddagger 13.25 ± 0.14 kcal mol $^{-1}$, ΔS^\ddagger $+2.8 \pm 0.6$ cal mol $^{-1}$ K $^{-1}$ ³⁴³) and later to a slow nitrogen inversion.³⁴³ A summary of ΔG° and ΔG^\ddagger values for **432** from the ^1H -NMR is given in Fig. 17.

Recently, a variable-temperature study of the ^{13}C -NMR of 3,4-dimethyl-hexahydro-1,3,4-oxadiazine and of the trans-fused derivative **434** have completely clarified the conformational equilibria and allowed a rather complete energy contour to be constructed for the monocyclic oxadiazine (Fig. 17).³⁴⁴ The conformational analysis of other methyl-substituted tetrahydro-1,3,4-oxadiazines^{345,346} is consonant with these results.

The ^1H -NMR spectrum of perhydropyridazino[1,2-*c*][1,3,4]oxadiazine at -65°C is consistent with a predominance (ΔG° $\text{trans-435} \rightleftharpoons \text{cis-436}$ 0.4 kcal mol $^{-1}$ at -65°C) of the trans-fused conformation. The conformers were identified on the basis of J_{gem} values for the NCH_2O protons (**435**, $J_{\text{gem}} -7.9$ Hz; **436**, $J_{\text{gem}} -10.0$ Hz) (see values for locked compounds in Table V).³⁴⁷ Thus although **435** is destabilized by the anomeric effect and the anti-coplanar 1,2-lone pairs, these interactions are not sufficient to outweigh the two gauche-butane interactions and the one gauche-propanol interaction present in **436**. This conformational preference is also observed in the vapor phase by photoelectron spectroscopy.³⁴⁸ The magnitudes of ΔG^\ddagger (**435** \rightarrow transition state) and ΔG^\ddagger (**436** \rightarrow transition state) were evaluated as 15.0 kcal mol $^{-1}$ and 14.6 kcal mol $^{-1}$, respectively.³⁴⁷



³⁴³ F. G. Riddell and A. J. Kidd, *J. C. S. Perkin II*, 1816 (1977).

³⁴⁴ A. R. Katritzky, R. C. Patel, F. M. S. Brito-Palma, F. G. Riddell, and E. S. Turner, *Isr. J. Chem.* **20**, 150 (1980).

³⁴⁵ A. A. Potekhin and B. D. Zaitsev, *Khim. Geterotsikl. Soedin.*, 301 (1971).

³⁴⁶ A. A. Potekhin and Ye. A. Bogan'Kova, *Khim. Geterotsikl. Soedin.*, 1461 (1973).

³⁴⁷ V. J. Baker, A. R. Katritzky, and F. M. S. Brito-Palma, *Heterocycles* **8**, 451 (1977).

³⁴⁸ A. R. Katritzky, V. J. Baker, F. M. S. Brito-Palma, R. C. Patel, G. Pfister-Guillouzo, and C. Guimon, *J. C. S. Perkin II*, 91 (1980).

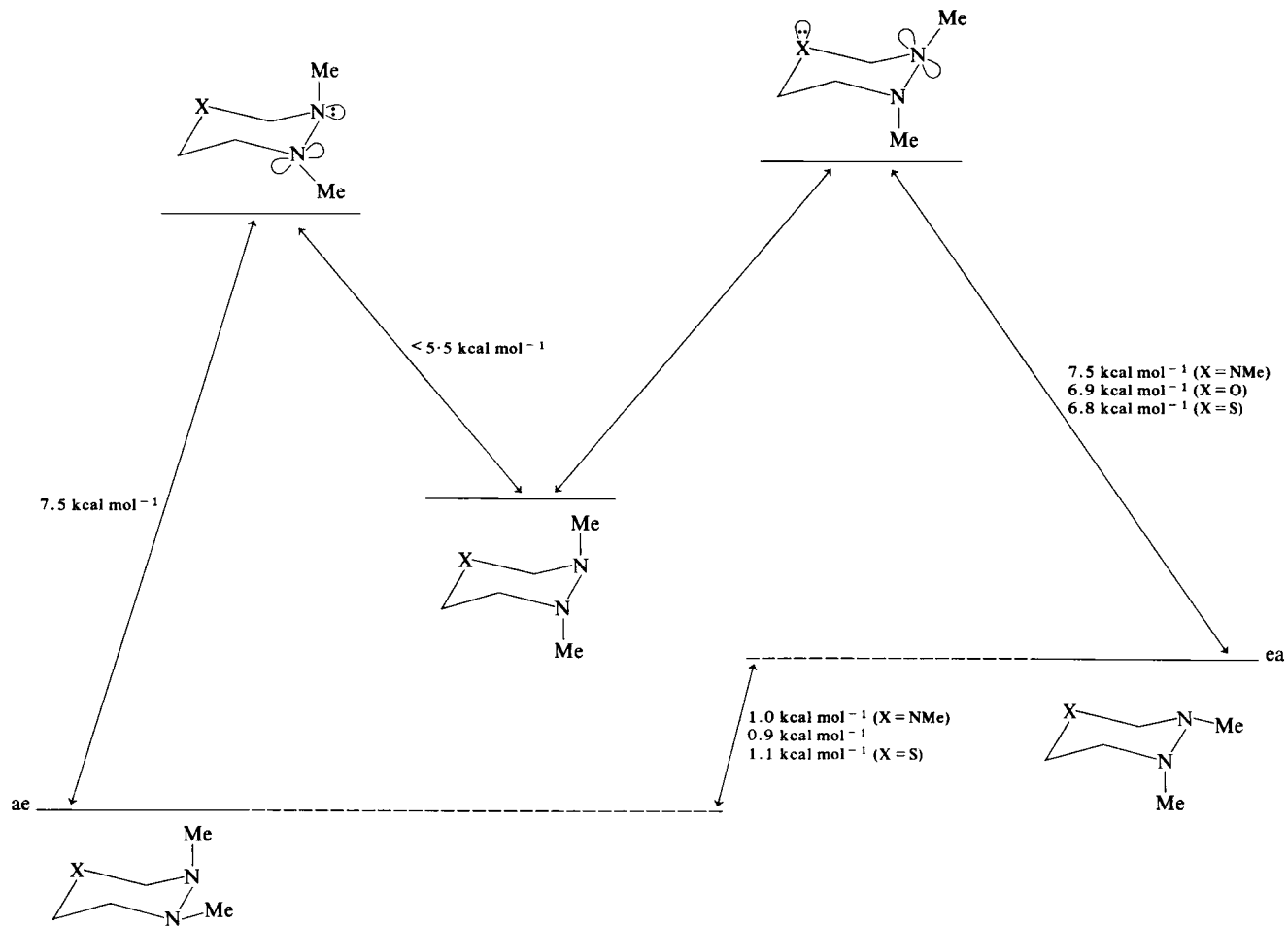


FIG. 17. ΔG° and ΔG^\ddagger for *N,N*-dimethyltetrahydro-1,3,4-oxadiazine (X = O), *N*-methyltetrahydro-1,3,4-thiadiazine (X = S) and 1,2,4-trimethylhexahydro-1,2,4-triazine (X = NMe).²

3. *Hexahydro-1,2,4-triazines*

The conformational equilibria for 1,2,4-trimethylhexahydro-1,2,4-triazine (**437**) are depicted in Fig. 16.⁹⁶ The conformational processes fall into slow passing inversions (crossing vertical line in Fig. 16) and the fast nonpassing inversions discussed for hexahydropyridazine (Section III,C,2) and for *N,N*-dimethyltetrahydro-1,3,4-oxadiazine (Section III,F,2). Furthermore, the additional low energy barrier processes depicted in Fig. 18 for inversion at N-4 must also be considered. NMR measurements, in fact, show the predominant existence of **437** in the eae conformation **438**,⁹⁶ and this is also predominant in the vapor phase (photoelectron spectroscopy).³⁴⁸ ¹³C-NMR spectra show a passing inversion ($\Delta G^\ddagger \sim 12 \text{ kcal mol}^{-1}$ at -31°C), which could not be unambiguously assigned, and a nonpassing nitrogen inversion ($\Delta G^\ddagger 7.5 \text{ kcal mol}^{-1}$ at -95°C). Estimates of ΔG_c° gave $1.20 \pm 0.1 \text{ kcal mol}^{-1}$ at -15°C , representing $\sim 10\%$ of eee **439** \rightleftharpoons eea **440** and $\sim 90\%$ eae

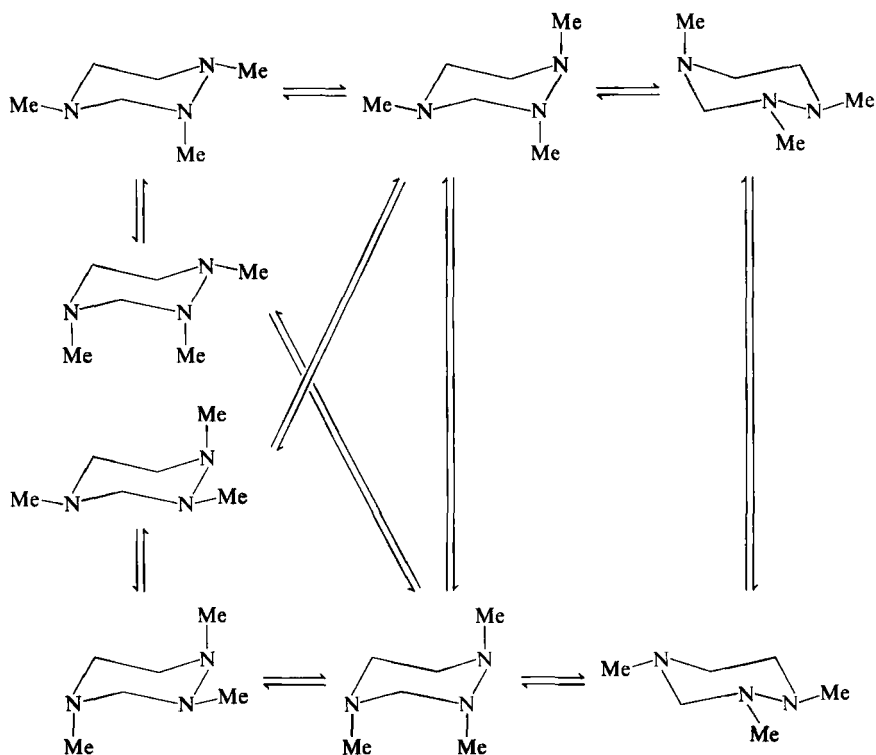
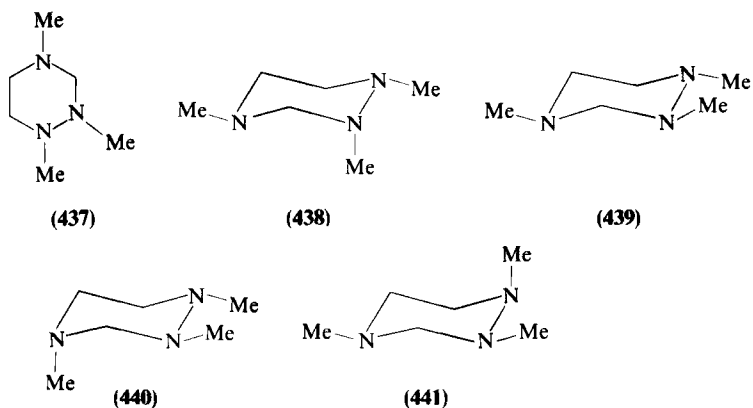


FIG. 18. Conformational interconversions in 1,2,4-trimethylhexahydro-1,2,4-triazine (no passing conversion shown: diagram corresponds to left-hand half of Fig. 16).⁹⁶



438, and 1.0 ± 0.1 kcal mol⁻¹ at -95°C in favor of 95% eae **438** with $\sim 5\%$ aee **441**.⁹⁶ A survey of ΔG° and ΔG^\ddagger values for **437** is given in Fig. 17.

The eae conformer **442** is favored by 1,2,3,4-tetramethylhexahydro-1,2,4-triazine: at 15°C a barrier of 12.2 kcal mol⁻¹ for the ring-inversion process is observed, and at -92°C there is a nonpassing nitrogen inversion process with ΔG^\ddagger 7.8 kcal mol⁻¹ (see Fig. 19).⁹⁶

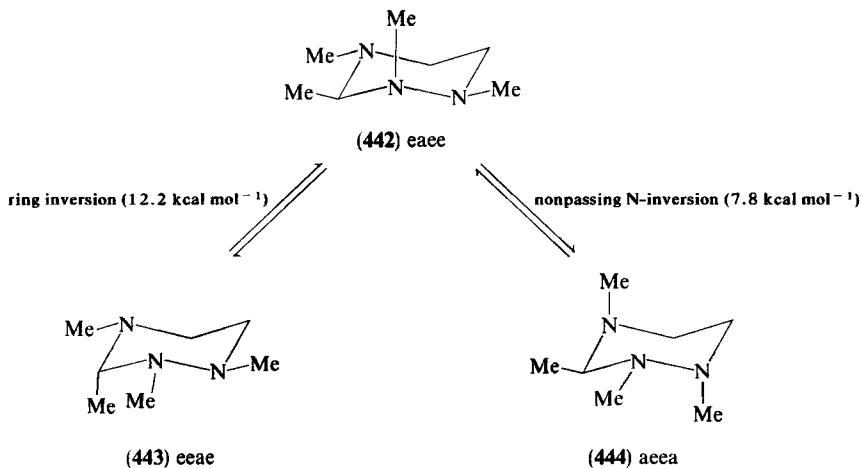


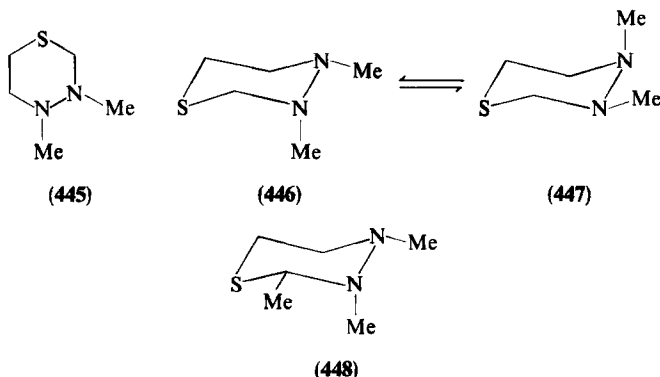
FIG. 19. Ring-inversion and nitrogen-inversion processes in 1,2,3,4-tetramethylhexahydro-1,2,4-triazine.⁹⁶

4. Tetrahydro-1,3,4-thiadiazines^{313,349}

The conformational equilibria for 3,4-dimethyltetrahydro-1,3,4-thiadiazine (**445**) is shown in Fig. 16 with slow passing inversion crossing the vertical

³⁴⁹ A. R. Katritzky and R. C. Patel, *J. C. S. Perkin II*, 279 (1980).

line (see discussion for *N,N*-dimethylhexahydropyridazine, Section III,C,2). The $^1\text{H-NMR}$ spectra give ΔG^\ddagger 12.7 kcal mol $^{-1}$ at -5°C for the lowest energy passing ring-inversion or N-inversion barrier, and $^{13}\text{C-NMR}$ spectra gave ΔG_c^\ddagger 6.7 ± 0.2 kcal mol $^{-1}$ at -113 to -116°C for the nonpassing nitrogen-inversion barrier $446 \rightleftharpoons 447$ with ΔG° for the equilibrium of 1.1 ± 0.1 kcal mol $^{-1}$ at -113 to -116°C , favoring **446** (see summary in Fig. 17).



Merely on the basis of electronegativity, the generalized anomeric effect would predict an increasing amount of ae conformer in the $ae \rightleftharpoons ea$ equilibrium for compounds of the type of Fig. 16 in the order $X = \text{NR} \simeq \text{S} < \text{O}$. The order actually found (e.g., Fig. 17) is $\text{O} \leq \text{N-Me} \leq \text{S}$ and reflects distortion in the S-containing ring. For the $\text{N-Me}_{\text{eq}} \rightleftharpoons \text{N-Me}_{\text{ax}}$ equilibrium in *N*-methyltetrahydro-1,3-thiazine, ΔG° is -0.7 kcal mol $^{-1}$ at $\sim -100^\circ\text{C}$, as opposed to $\Delta G^\circ -0.10$ kcal mol $^{-1}$ at similar temperatures for *N*-methyltetrahydro-1,3-oxazine. This leads to the expectation that the percentage of axial 3-N Me conformer in the **445** equilibrium will be greater than in the corresponding equilibrium for *N,N*-dimethyltetrahydro-1,3,4-oxadiazine (**432**) (Section III,E,2), which is in fact observed.³⁴⁹

Photoelectron studies show **446** to predominate in the vapor phase.³⁴⁸

The predominant conformation of 2,3,4-trimethyl-1,3,4-thiadiazine was shown to be **448**; this exists in equilibrium with a minor 2ax-3eq-4eq conformer. 2,2,3,4-Tetramethyl-1,3,4-thiadiazine exist as the 3ax-4eq conformer as expected.³⁴⁹

5. Tetrahydro-1,2,4-oxadiazines

^{13}C - and ^1H -NMR measurements³⁵⁰ have permitted a complete description of the conformational equilibria for 2,4-dimethyltetrahydro-1,2,4-oxadiazine (**449**), and this is summarized in Fig. 20. As expected from the

³⁵⁰ F. G. Riddell, E. S. Turner, A. R. Katritzky, R. C. Patel, and F. M. S. Brito-Palma, *Tetrahedron* **35**, 1391 (1979).

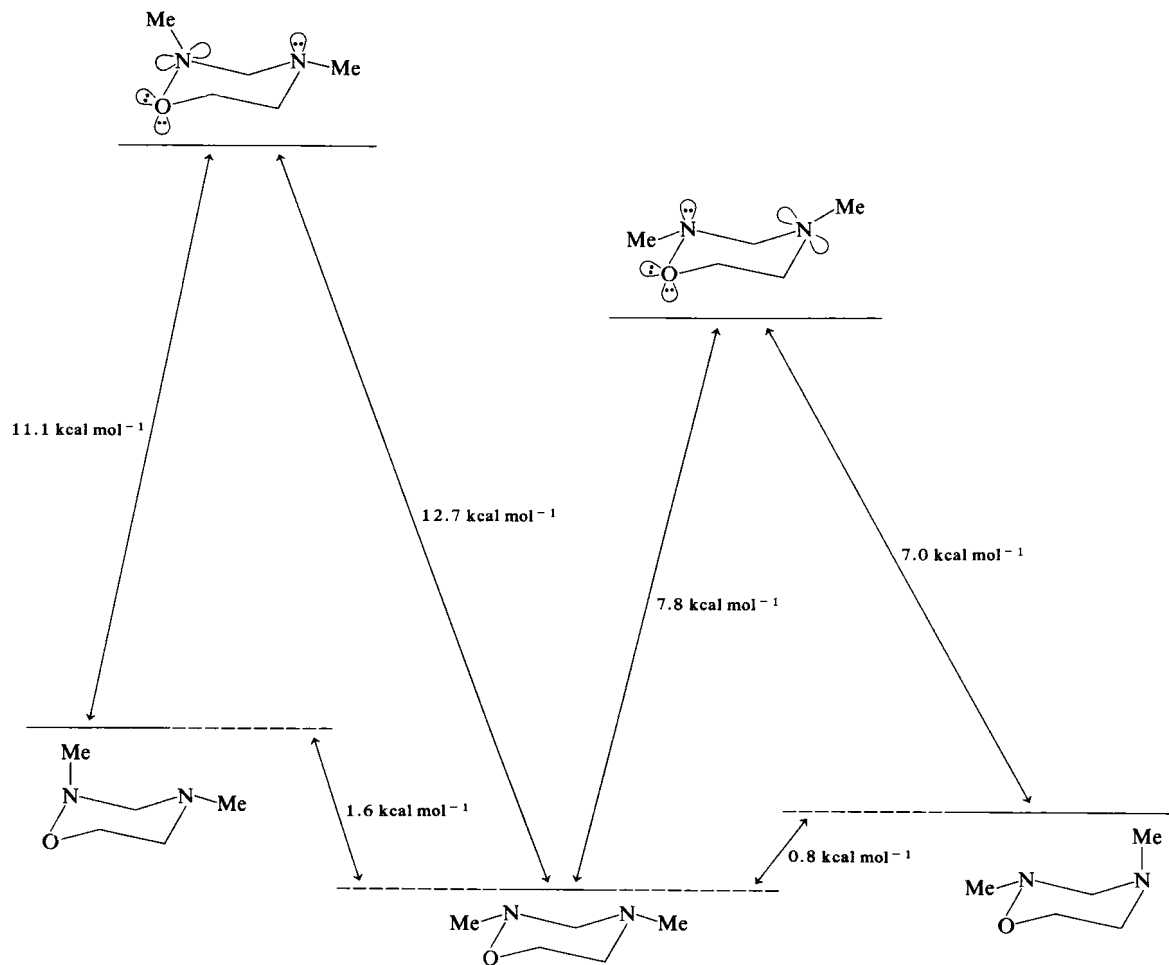
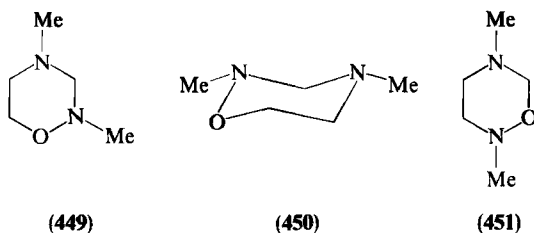


FIG. 20. ΔG° and ΔG^\ddagger for 2,4-dimethyltetrahydro-1,2,4-oxadiazine.³⁵⁰

high conformational preference for $N\text{-Me}_{\text{eq}}$ in $N\text{-methyltetrahydro-1,2-oxazine}$ and for the preference for ee in $N,N\text{-dimethylhexahydropyrimidine}$, the ee **450** conformer is favored.



Variable-temperature ^{13}C -NMR studies of 2,4,6-trimethyltetrahydro-1,2,4-oxadiazine also show two coalescences. At low temperature, $\Delta G^\circ = 0.6 \text{ kcal mol}^{-1}$ and $\Delta G_{\text{ax} \rightarrow \text{ts}}^\ddagger = 6.8 \text{ kcal mol}^{-1}$ for inversion at the 4- $N\text{-Me}$ (eee conformer preferred). Study of the 2-isopropyl-4-methyl derivative shows that it is easier to place the 2-isopropyl group axial ($\Delta G^\circ 1.2 \text{ kcal mol}^{-1}$) than the 2-methyl group in the analog **451** ($\Delta G^\circ 1.6 \text{ kcal mol}^{-1}$).³⁵⁰

6. Tetrahydro-1,2,5-oxadiazines

The conformational equilibria in $N,N\text{-dimethyltetrahydro-1,2,5-oxadiazine}$ **451** (Fig. 21) may be considered with reference to those of the $N\text{-methyltetrahydro-1,2-oxazine}$ system (Section III,C,1) (for which $\Delta G^\circ 3.7 \text{ kcal mol}^{-1}$ favors $N\text{-Me}_{\text{eq}}$) and the $N\text{-methyltetrahydro-1,3-oxazine}$ system (Section III,D,1) ($\Delta G^\circ 0.1 \text{ kcal mol}^{-1}$ favors $N\text{-Me}_{\text{ax}}$). Hence the 2- $N\text{-Me}$ group should be predominantly equatorial and the 5- $N\text{-Me}$ should show a small preference for the axial orientation.

^1H -NMR variable-temperature studies of 2,5-dimethyltetrahydro-1,2,5-oxadiazine^{351–354} established a high energy barrier process ($\Delta G^\ddagger 14.4 \pm 0.1 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger -1.2 \pm 0.4 \text{ kcal mol}^{-1}$) comparable to that in $N\text{-methyltetrahydro-1,2-oxazine}$. From studies of a deuterated tetrahydro-1,2-oxazine, it was concluded that this should be attributed to slowing of 2- $N\text{-Me}$ inversion rather than ring reversal.³⁵³

From ^{13}C NMR,^{351,354} a lower barrier of $7.7 \pm 0.2 \text{ kcal mol}^{-1}$ was assigned to N-5-Me inversion: $\Delta G^\circ 0.31 \pm 0.05 \text{ kcal mol}^{-1}$ at -136°C favors the N-5 axial conformer **452**.

³⁵¹ A. R. Katritzky and R. C. Patel, *Heterocycles* **9**, 263 (1978).

³⁵² F. G. Riddell and E. S. Turner, *Heterocycles* **9**, 267 (1978).

³⁵³ F. G. Riddell and E. S. Turner, *J. Chem. Res., Synop.*, 476 (1978).

³⁵⁴ A. R. Katritzky and R. C. Patel, *J. C. S. Perkin II*, 993 (1979).

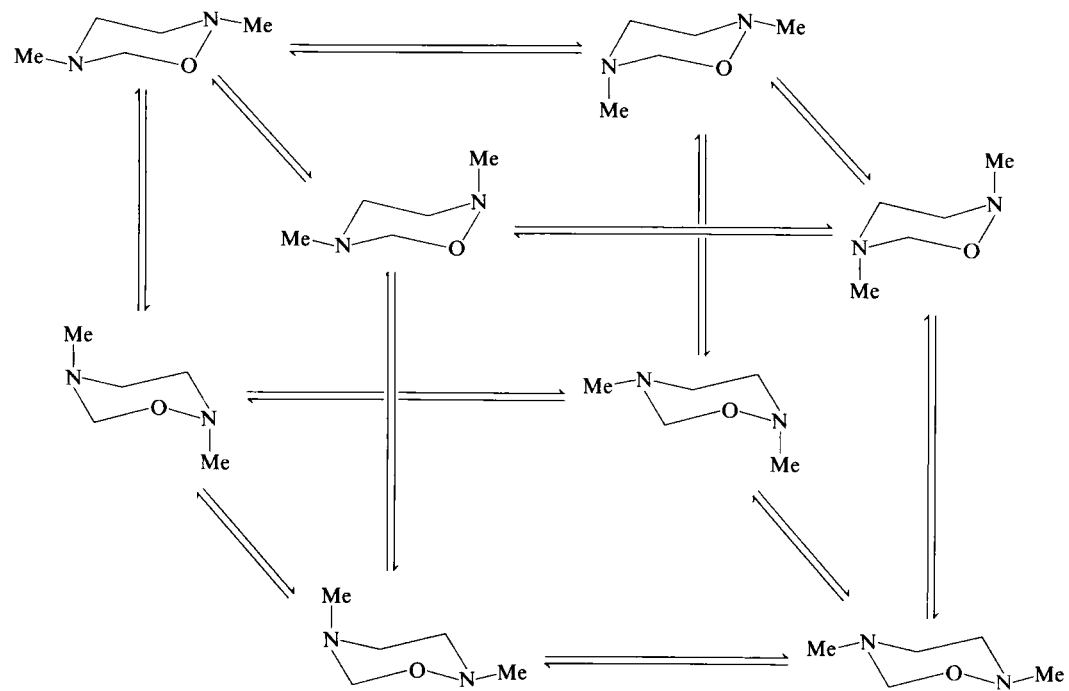
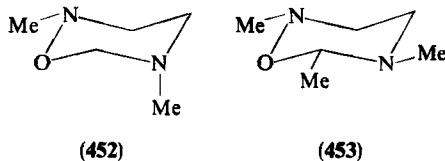


FIG. 21. Conformational equilibria for 2,5-dimethyltetrahydro-1,2,5-oxadiazine.

The conformational equilibria of 2,5,6-tri- and 2,5,6,6-tetramethyltetrahydro-1,2,5-oxadiazine were also studied.³⁵⁴ These compounds show a high-energy barrier at ~ 14 kcal mol⁻¹ together with 5-N—Me inversion barriers of 8.2 and 7.7 kcal mol⁻¹. The insertion of a 2-CMe into the 1-oxa-3-aza system displaces the 3-NMe equilibrium toward the 3-NMe equatorial conformer (cf. ΔG° 0.10 kcal mol⁻¹ favoring **453** for 2,5,6-trimethyltetrahydro-1,2,5-oxadiazine).



G. 1,3,5-HETEROCYCLIC SYSTEMS

1. Dihydro-1,3,5-dioxazines

In the conformational equilibrium (Fig. 22) for 5-methyldihydro-1,3,5-dioxazine (**454**) the generalized anomeric effect favors the *N*-Me_{ax} conformer **455** and, in addition (relative to *N*-Me_{ax} piperidine), **455** does not contain the two unfavorable syn-axial interactions involving the axial *N*-methyl

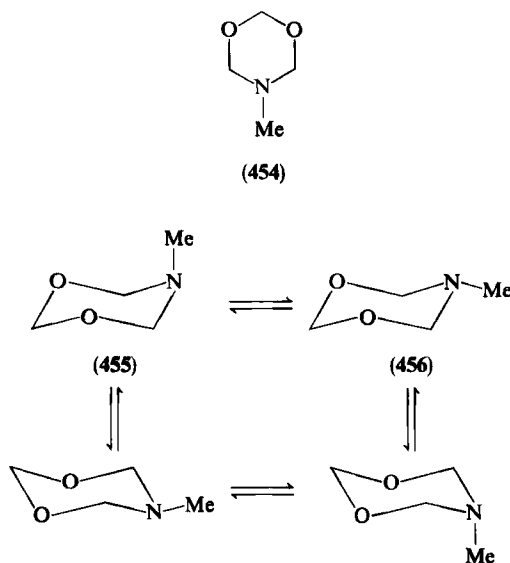


FIG. 22. Conformational equilibrium for 5-methyldihydro-1,3,5-dioxazine.

group in *N*-methylpiperidine. Accordingly, **455** should be highly favored, and this is found³⁵⁵ to be the case; no change is observed in the ¹³C-NMR spectrum over the range +34 to -145°C. The $J_{\text{gem}}(\text{NCH}_2\text{O})$ of -10 Hz in the ¹H-NMR spectrum is also consonant with **455** (see Table V). A value for ΔG^\ddagger of 10.5 kcal mol⁻¹ at -58°C is observed for the ring-inversion process.³⁵⁵

The successive change in position of the $\text{N-Me}_{\text{ax}} \rightleftharpoons \text{N-Me}_{\text{eq}}$ equilibrium from that in 5-methyldihydro-1,3,5-dioxazine ($\Delta G^\circ > 1$ kcal mol⁻¹) to 3-methyltetrahydro-1,3-oxazine ($\Delta G^\circ 0.10 \pm 0.05$ at -120°C) to that ($\Delta G^\circ -2.7$ kcal mol⁻¹) in 1-methylpiperidine results from successive differences of syn-axial interactions involving the axial methyl group and a favoring of the axial methyl conformer by the generalized anomeric effect.

2. Tetrahydro-1,3,5-oxadiazines

The conformational equilibrium (Fig. 23) for *N,N*-dimethyltetrahydro-1,3,5-oxadiazine (**457**) is suggested by a priori considerations similar to those discussed above (Section III,G,1) for the dihydro-1,3,5-dioxazine system to

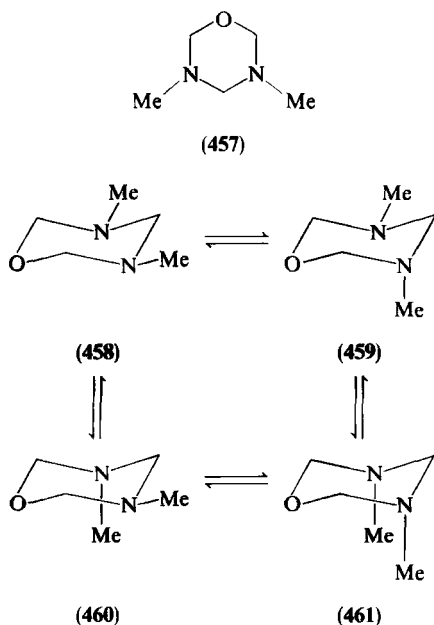


FIG. 23. Conformational equilibrium for 3,5-dimethyltetrahydro-1,3,5-oxadiazine.

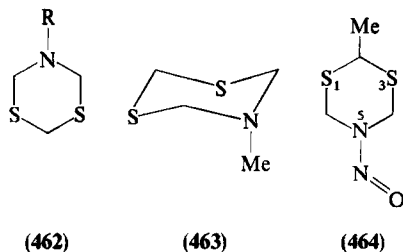
³⁵⁵ V. J. Baker, I. J. Ferguson, A. R. Katritzky, R. C. Patel, and S. Rahimi-Rastgoo, *J. C. S. Perkin II*, 377 (1978).

favor the predominance of the *ae* conformer **459**, and this is confirmed by experiment.³⁵⁵ A value for ΔG^\ddagger for the ring-inversion process was calculated as $11.2 \text{ kcal mol}^{-1}$ at -43°C and ΔG^\ddagger for nitrogen inversion as $6.8 \pm 0.4 \text{ kcal mol}^{-1}$ at -140°C . The low temperature $^1\text{H-NMR}$ spectrum gives $J_{\text{gem}}(\text{OCH}_2\text{N}) - 10 \text{ Hz}$ and $J_{\text{gem}}(\text{NCH}_2\text{N}) - 10.0 \text{ Hz}$, consonant with the *ae* conformer **459**. The energetics of the conformational equilibrium is depicted in Fig. 24.

3. Dihydro-1,3,5-dithiazines

The difference in conformational free energy of the *N*-Me group in *N*-methylpiperidine ($2.7 \text{ kcal mol}^{-1}$, favoring *N*-Me_{eq}) and in *N*-methyltetrahydro-1,3-thiazine ($0.7 \text{ kcal mol}^{-1}$, favoring *N*-Me_{ax} at -120°C) suggests the predominance of the *N*-Me_{ax} conformer **463** of 5-methyldihydro-1,3,5-dithiazine (**462**; R = Me). Indeed, $^1\text{H-NMR}$ spectra and dipole-moment data show that NR axial is the predominant conformer for a series of *N*-alkyldihydro-1,3,5-dithiazines (**462**; R = Me, Et, *i*Pr, *t*-Bu).³⁵⁶ This even applies to the *N*-*tert*-butyl compound, which possesses an unconstrained axial *tert*-butyl group.³⁵⁷

Ring-inversion barriers decrease in these compounds with increasing size of the *N*-alkyl group (**462**; R = Me, ΔG^\ddagger 10.9 ± 0.2 ; R = *i*Pr, ΔG^\ddagger 10.4 ± 0.2 ; and R = *t*-Bu, ΔG^\ddagger $9.3 \pm 0.3 \text{ kcal mol}^{-1}$).³⁵⁶ A boat conformation has been suggested³⁵⁸ for one of the isomeric 2,4,5,6-tetramethyldihydro-1,3,5-dithiazines.



Variable temperature $^1\text{H-NMR}$ spectra of 5-nitroso-2,4,6-trimethyl-5,6-dihydro-4*H*-1,3,5-dithiazine (**464**) (all three methyl groups shown to be *cis* by X-ray crystallography) gave an unusually low barrier to rotation about the N—N bond ($17.2 \text{ kcal mol}^{-1}$) attributed to the electron-withdrawing sulfur substituents and steric crowding.³⁵⁹

³⁵⁶ L. Angiolini, R. P. Duke, R. A. Y. Jones, and A. R. Katritzky, *J. C. S. Perkin II*, 674 (1972).

³⁵⁷ L. Angiolini, R. P. Duke, R. A. Y. Jones, and A. R. Katritzky, *Chem. Commun.*, 1308 (1971).

³⁵⁸ G. G. Butenko, A. N. Vereshchagin, and B. A. Arbuzov, *Khim. Geterotsikl. Soedin.*, 321 (1972).

³⁵⁹ T. J. Hansen, R. M. Angeles, L. K. Keefer, C. S. Day, and W. Gaffield, *Tetrahedron* **37**, 4143 (1981).

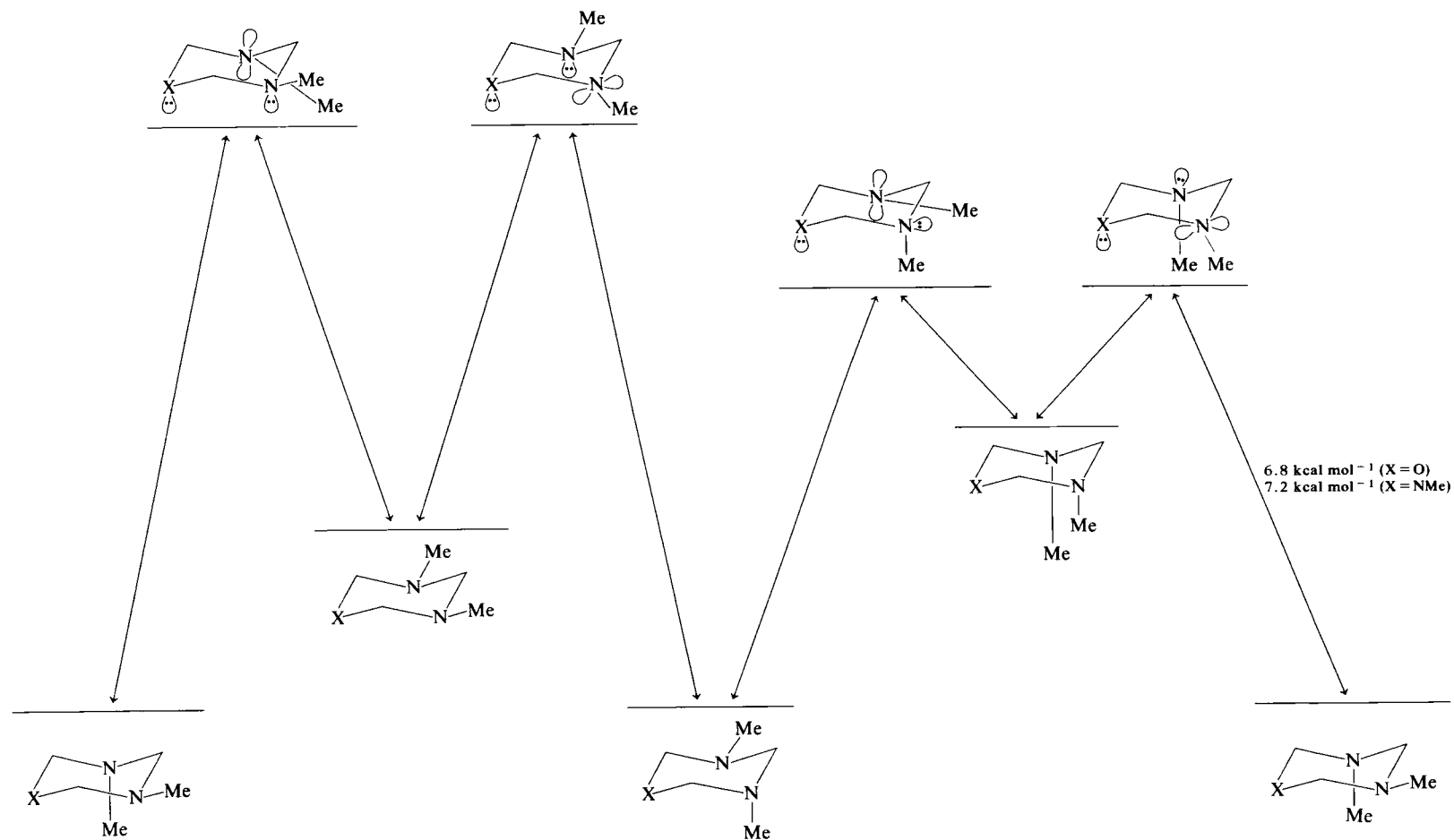
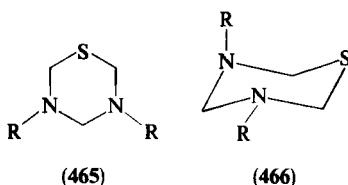


FIG. 24. Inversion barriers in 3,5-dimethyltetrahydro-1,3,5-oxadiazine (X = O) and in 1,3,5-triethylhexahydro-1,3,5-triazine (X = NMe).³¹⁹

4. Tetrahydro-1,3,5-thiadiazines

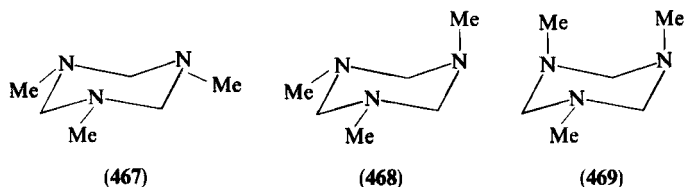
By analogy with the tetrahydro-1,3,5-oxadiazine system, the ae conformer **466** of 3,5-dialkyltetrahydro-1,3,5-thiadiazines (**465**) should predominate in the conformational equilibrium. Investigation of a series of 3,5-dialkyl derivatives by $^1\text{H-NMR}$ disclosed ring-inversion barriers that decrease with increasing size of the substituent (**465**: $\text{R} = \text{Me}$, ΔG^\ddagger 12.1 ± 0.3 ; $\text{R} = \text{Et}$, ΔG^\ddagger 12.0 ± 0.2 ; $\text{R} = i\text{Pr}$, ΔG^\ddagger 10.5 ± 0.4 kcal mol^{-1}). No further changes in the $^1\text{H-NMR}$ spectra on cooling were found. Dipole-moment data indicated that all the compounds existed predominantly in the ae conformation.³⁵⁶ It is difficult to draw conclusions for J_{gem} in this series.

In the 3,5-diethyl compound, slow ring inversion renders the CH_2 protons of the ethyl groups nonequivalent, and appropriate coalescence phenomena are observed.³⁶⁰



5. Hexahydro-1,3,5-triazines

In contrast to the other 1,3,5-trihetero systems just discussed, it is now believed that the conclusions originally reached^{361,362} regarding the conformations of 1,3,5-trialkylhexahydro-1,3,5-triazines (**467–469**) are misleading; it is no longer believed that di-N-axial conformations are appreciably populated for the trimethyl and triethyl derivatives.



³⁶⁰ L. Angiolini, R. A. Y. Jones, and A. R. Katritzky, *Tetrahedron Lett.*, 2209 (1971).

³⁶¹ R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc. B*, 135 (1970).

³⁶² R. P. Duke, R. A. Y. Jones, A. R. Katritzky, R. Scattergood, and F. G. Riddell, *J. C. S. Perkin II*, 2109 (1973).

It is to be expected that among the possible conformers **467**–**469** of 1,3,5-trimethylhexahydro-1,3,5-triazine, **468** should predominate. Conformer **468** is favored by the generalized anomeric effect and the two unfavorable syn-axial interactions present in axial *N*-methylpiperidine are replaced by the energetically less demanding gauche-propylamine interactions. Indeed, the ^1H -NMR spectrum at -140°C shows two AB quartets ($J_{\text{NCH}_2\text{N}} -7.9$ and -10.7 Hz) consonant (see Table V) with **468**.³⁶³ Application of ^{13}C -NMR spectra³⁵⁵ confirms the result for the trimethyl compound and suggests that the triethyl and triisopropyl analogs also exist in the monoaxial diequatorial conformations (cf. **468**). ^{13}C - and ^1H -NMR spectra lead to a similar conclusion for 1,3,5-trimethoxyhexahydro-1,3,5-triazine.³⁶⁴

From the ^1H -NMR spectra the barrier to ring inversion was estimated as $\Delta G^\ddagger 13.2 \pm 0.2 \text{ kcal mol}^{-1}$ at -5°C and the barrier to *N*-inversion as $\Delta G^\ddagger 7.2 \pm 0.1 \text{ kcal mol}^{-1}$ at -123.5°C .³⁶³ Barriers to ring inversion in 1,3,5-trialkyl derivatives **470** decrease with increasing size of substituent,^{297,365,366} and ΔG^\ddagger values for nitrogen inversion (determined by ^{13}C -NMR spectroscopy³⁵⁵) follow a similar trend (Table XXIX). The barriers to *N*-inversion

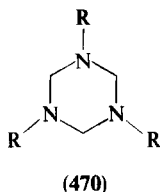


TABLE XXIX
RING INVERSION AND *N*-INVERSION BARRIERS IN 1,3,5-
TRIALKYLHEXAHYDRO-1,3,5-triazines³⁵⁵

Compound	Ring inversion ΔG^\ddagger (kcal mol $^{-1}$)	<i>T</i> ($^\circ\text{C}$)	<i>N</i> -inversion ΔG^\ddagger (kcal mol $^{-1}$)	<i>T</i> ($^\circ\text{C}$)
470 : R = Me	12.8	−9	7.15	−125
R = Et	11.4	−22	6.80	−130
R = <i>i</i> Pr	11.0	−41	5.99	−140
R = <i>t</i> -Bu	10.2	−54	—	—

³⁶³ C. H. Bushweller, M. Z. Lourandos, and J. A. Brunelle, *J. Am. Chem. Soc.* **96**, 1591 (1974).

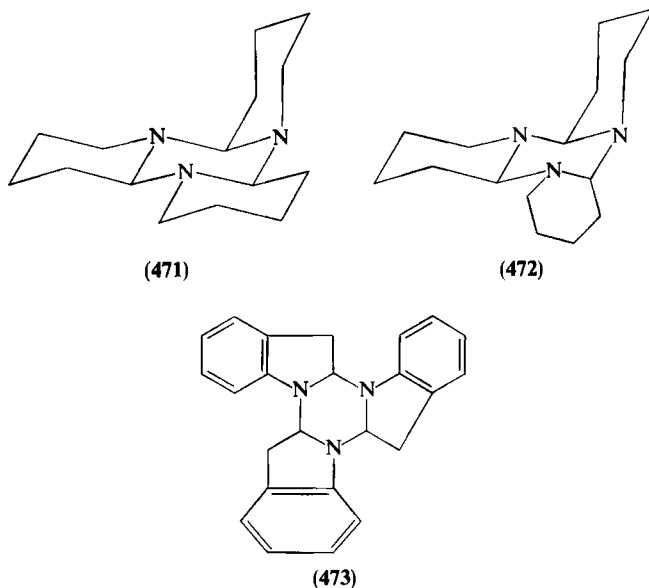
³⁶⁴ I. J. Ferguson, A. R. Katritzky, and S. Rahimi-Rastgoo, *Gazz. Chim. Ital.* **107**, 363 (1977).

³⁶⁵ F. G. Riddell and J. M. Lehn, *Chem. Commun.*, 376 (1966).

³⁶⁶ J. M. Lehn, F. G. Riddell, B. J. Price, and I. O. Sutherland, *J. Chem. Soc. B*, 387 (1967).

are depicted in Fig. 24: it is suggested that the observed interconversion of two equivalent forms may occur more easily via the di-N-axial than via the di-N-equatorial conformer.³⁵⁵

The predominant conformations of α -tripiperidine **471** and β -tripiperidine **472** are also those with one axial N-alkyl substituent. The ΔG^\ddagger of 11.2 ± 0.1 kcal mol⁻¹ observed for interconversion in α -tripiperidine has been assigned to inversion of one ring and of a nitrogen atom.³⁶⁷ The structure of the trimer **473** from β,β -dimethylindolenine³⁶⁸ is now thought³⁶⁹ to be similar to that of β -tripiperidine.



H. TETRAHETEROCYCLIC SYSTEMS

1. Introduction and Early Work

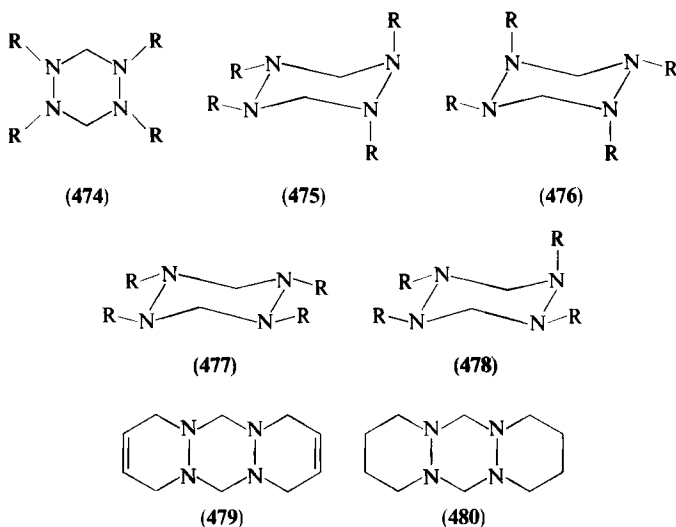
The conformational equilibria of the 1,2,4,5-tetraalkylhexahydro-1,2,4,5-tetrazines (**474**) and related fused-ring systems are the most complicated of the systems treated in this review. The elucidation of these equilibria and

³⁶⁷ H. Kessler and G. Zimmerman, *Chem. Ber.* **110**, 2306 (1977).

³⁶⁸ H. Fritz and P. Pfaender, *Chem. Ber.* **98**, 989 (1965).

³⁶⁹ H. Kessler, H. Möhrle, and G. Zimmermann, *J. Org. Chem.* **42**, 66 (1977).

the related kinetic parameters represent a fascinating story and a fitting climax to this account.



The early work can be summarized as follows: 1,2,4,5-tetramethylhexahydro-1,2,4,5-tetrazine (**474**; R = Me) possesses four chair conformations (**475**–**478**) not involving two axial groups on the same side of the ring and interconvertible by nitrogen inversion. The first publication concerned the ^1H -NMR spectrum of **474** (R = Me) at -87°C , which showed an AB quartet for the NCH_2N protons and a 1:1 doublet for the methyl groups and was interpreted as indicating **476**.³⁷⁰ However, a consideration of intramolecular interactions and dipole moment work supported the alternative conformation **475**.³⁷¹ Next, comparison of low-temperature NMR spectra of **474** (R = Me) with spectra of **479** and **480** was thought to show that the original assignment **476** was correct, whereas the tetraethyl analog **474** (R = Et) existed mainly as **475** in equilibrium with $\sim 15\%$ of **476**.³⁷² However, the real situation turned out to be much more complex, and we need to introduce a new concept before considering the later work.

2. Concept of Conformational Sets

If ring inversions are assumed to be of high energy, then at temperatures where ring inversions and passing nitrogen inversions are slow but

³⁷⁰ J. E. Anderson and J. D. Roberts, *J. Am. Chem. Soc.* **90**, 4186 (1968).

³⁷¹ R. A. Y. Jones, A. R. Katritzky, and A. C. Richards, *Chem. Commun.*, 708 (1969).

³⁷² S. F. Nelsen and P. J. Hintz, *J. Am. Chem. Soc.* **94**, 3138 (1972).

nonpassing and nitrogen inversions fast (see Fig. 11 and discussion in Section III,C,2 concerning interconversions in *N,N*-dimethylhexahydropyridazine), monocyclic hexahydrotetrazines exist in four sets (A, B, and C, with the fourth set the mirror image of C) as shown in Fig. 25. In set B, three of the conformers that contain two axial groups in a 1,3-orientation are expected not to contribute appreciably to the equilibrium.

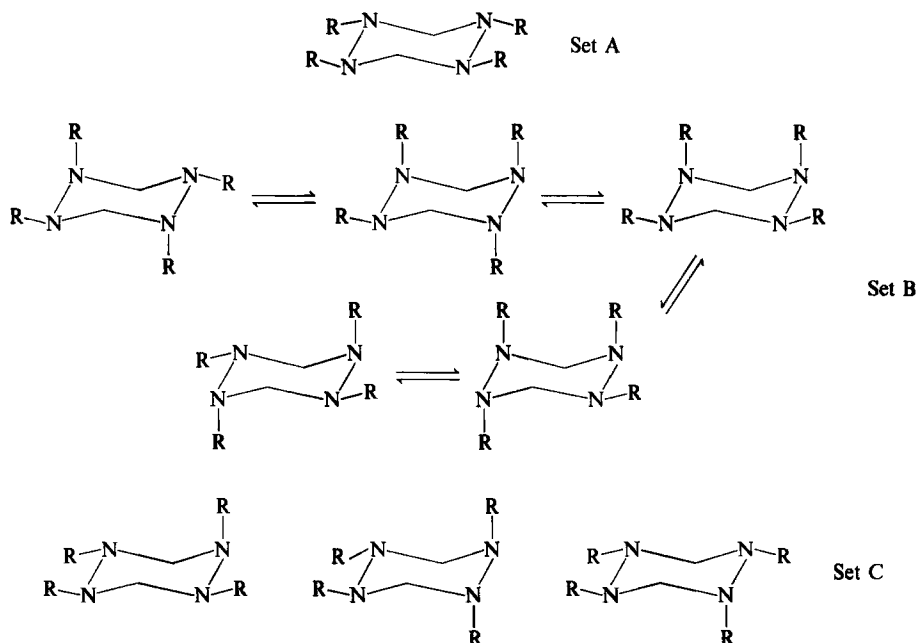


FIG. 25. Conformational equilibria for 1,2,4,5-tetraalkylhexahydro-1,2,4,5-tetrazines.³⁷³

Bicyclic and tricyclic hexahydrotetrazines can also exist in sets: four for the bicyclic and three for the tricyclic. The relationship of these sets to those for the monocyclic derivative is shown in Fig. 26.

Conclusive evidence for the conformational equilibria of the hexahydrotetrazines was obtained from a study of compounds with fused rings, particularly the tricyclic derivatives.

3. Conformation of Tricyclic Hexahydrotetrazines

Whereas the low-temperature spectrum of **479** is too complex for interpretation even at 220 MHz (Fig. 27a), the specifically deuterated derivative

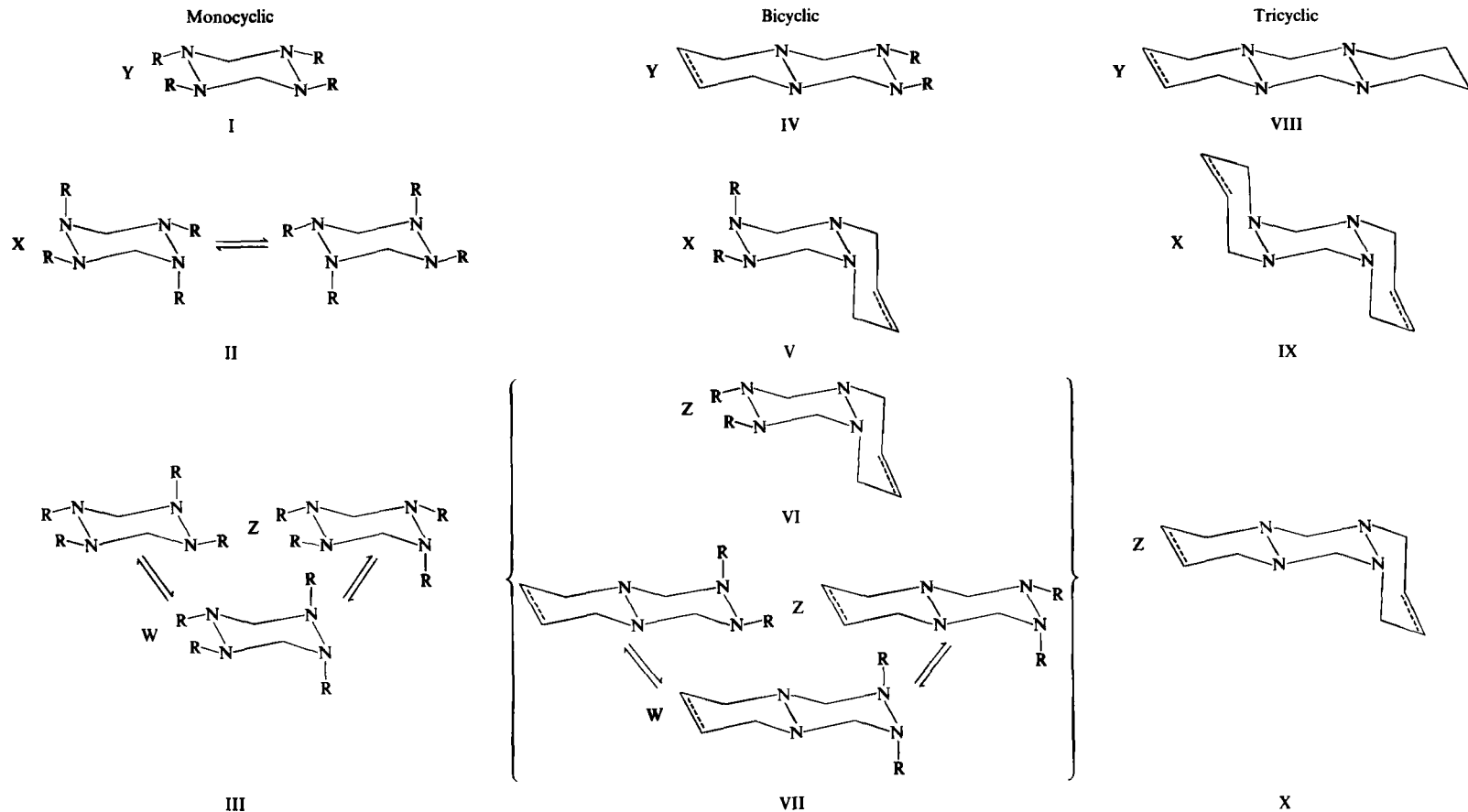


FIG. 26. Conformational sets and types of hexahydro-*s*-tetrazines. (Reprinted with permission from Ref. 374. Copyright 1976 American Chemical Society.)

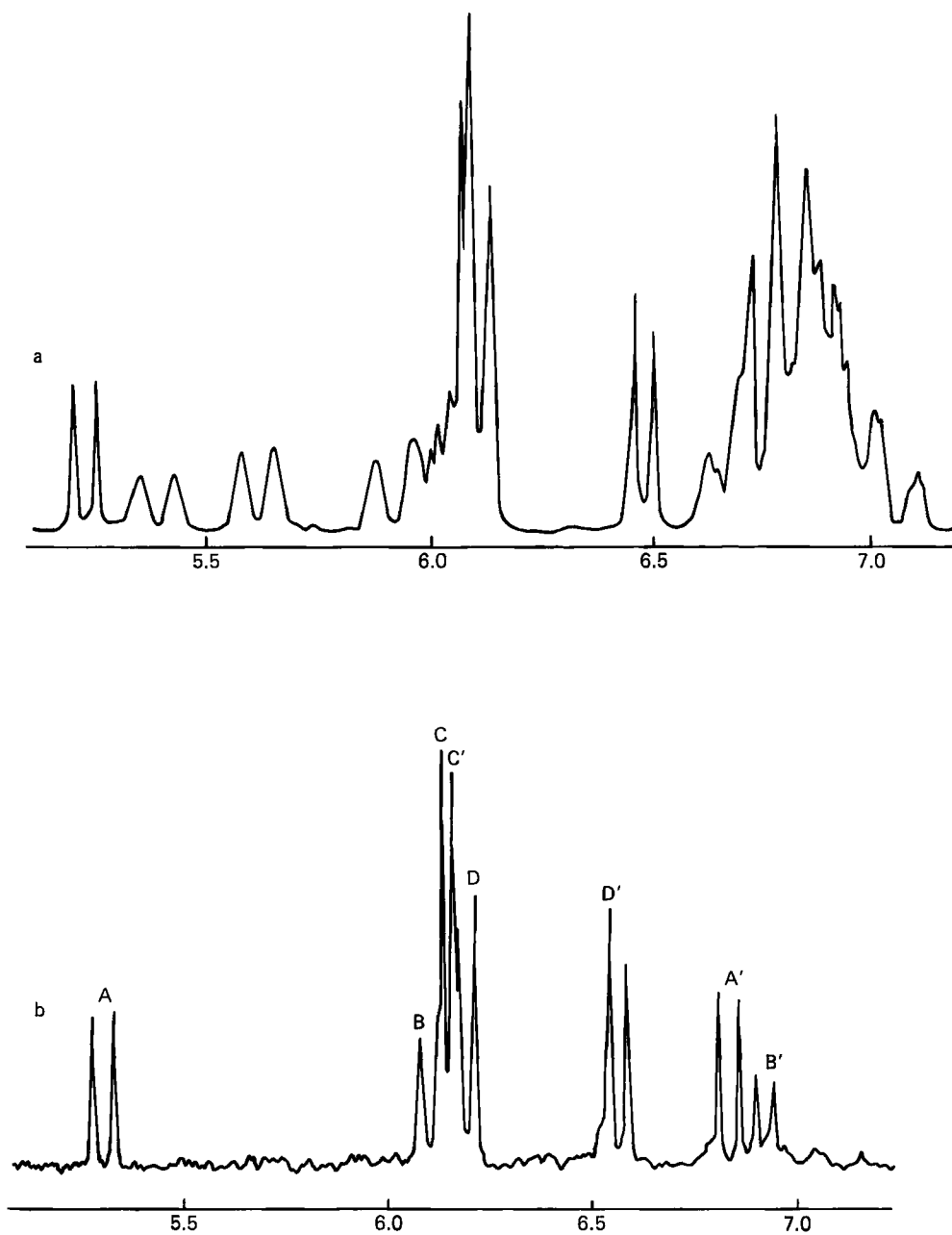
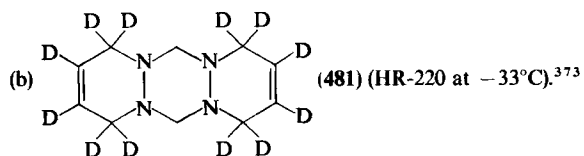
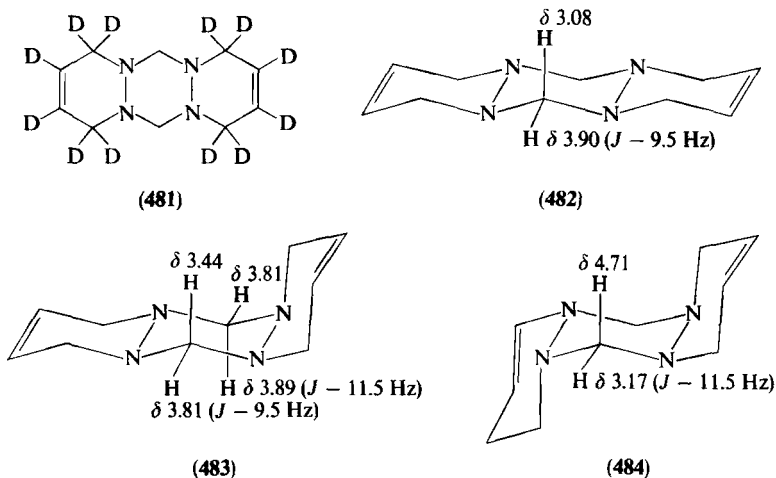


FIG. 27. ^1H -NMR spectra of (a) C1=CN2C=NC=CN2C1 (479) (HR-220 at -30°C) and



481 shows clearly the presence of four AB quartets (Fig. 27b). The symmetrical conformers X and Y (see Fig. 26) each give rise to a single quartet (**482** and **484**), whereas the unsymmetrical conformer Z gives two equal quartets (**483**).³⁷³ This interpretation was confirmed by the ¹³C-NMR spectrum: at 90°C, three singlets are observed for N—C—N, N—C—C and C=C=C. At -30°C these singlets split into 4, 7, and 6 peaks, respectively (Fig. 28) which (given one overlap) is just what is expected for the three conformers.³⁷⁴

In contrast, the saturated tricyclic compound **480** exists solely in the all-equatorial form Y.³⁷³



4. Conformations of Monocyclic and Bicyclic Hexahydrotetrazines

Based on the work just mentioned on the tricyclic analog, it has been possible to elucidate completely the conformational equilibria of a variety of monocyclic and bicyclic hexahydrotetrazines, using mainly ¹H-³⁷³ and ¹³C-NMR³⁷⁴ spectroscopy. For example, the low-temperature (-80°C) ¹H-NMR spectrum of the tetraethyl analog **474** (R = Et) shows two AB quartets for the NCH₂N protons: the major conformer **485** (80%) with $J_{\text{gem}} = 14.0$ Hz, $\Delta_{\text{ac}} = 1.7$ ppm and the minor conformer (20%) with $J_{\text{gem}} = 12.0$ Hz, $\Delta_{\text{ac}} = 0.31$ ppm, indicating 80% set B and 20% set C (Fig. 25).³⁷³ This has been confirmed by ¹³C-NMR spectroscopy.³⁷⁴

³⁷³ R. A. Y. Jones, A. R. Katritzky, A. R. Martin, D. L. Ostercamp, A. C. Richards, and J. M. Sullivan, *J. Am. Chem. Soc.* **96**, 576 (1974); *J. C. S. Perkin II*, 948 (1974).

³⁷⁴ V. J. Baker, A. R. Katritzky, J. P. Majoral, A. R. Martin, and J. M. Sullivan, *J. Am. Chem. Soc.* **98**, 5748 (1976).

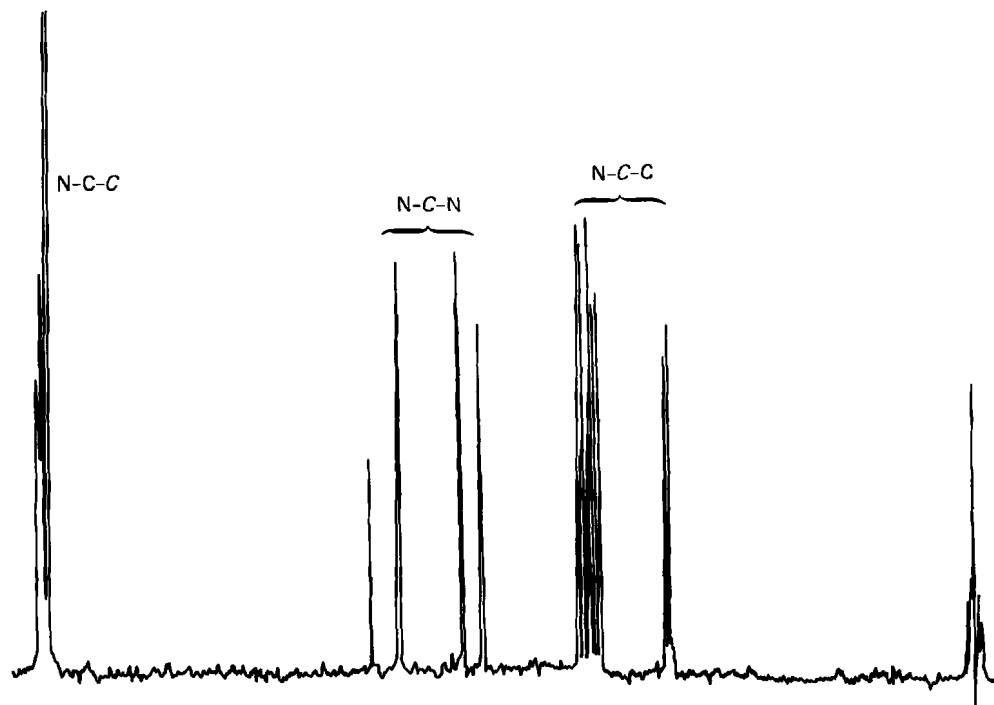
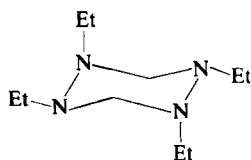
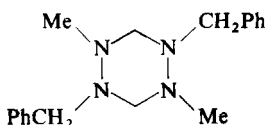


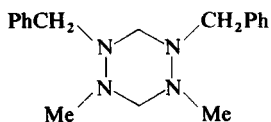
FIG. 28. ^{13}C -NMR spectrum of C1=CC2N3C=CC=CC3N2N1 at -30°C . (Reprinted with permission from Ref. 374. Copyright 1976 American Chemical Society.)



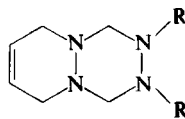
(485)



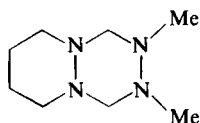
(486)



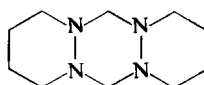
(487)



(488)



(489)



(490)

The results are summarized in Table XXX. It can be seen that the predominant conformation depends critically on the N-alkyl substituent,

TABLE XXX
CONFORMER POPULATIONS (%) OF HEXAHYDROTETRAZINES

Compound			Set ^a		
Structure	Ring	Substituent	I, IV, VIII	II, V, IX	III, VI, VII, X
474	Mono	Me ₄			100
474	Mono	Et ₄			20
474	Mono	iPr ₄	50 ^b	80	50
			60 ^c		40
474	Mono	Bz ₄		100	
486	Mono	Me ₂ Bz ₂ ; sym		35	65
487	Mono	Me ₂ Bz ₂ ; unsym		35	65
cf. 486	Mono	iPr ₂ Bz ₂ ; sym			100 ^d
488	Bi	Me ₂ ; unsat			100
488	Bi	Et ₂ ; unsat			100
488	Bi	iPr ₂ ; unsat			100
489	Bi	Me ₂ ; sat			100
479	Tri	Unsat	13	20	66
480	Tri	Sat	100		

^a See Fig. 26.

^b ¹H-NMR results.

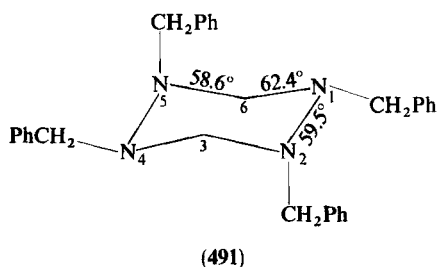
^c ¹³C-NMR results.

^d May be 50% I, 50% II.

being different for the Me_4 , Et_4 , and $i\text{Pr}_4$ derivatives. All the bicyclic derivatives exist exclusively as a single conformer set.

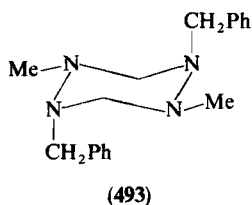
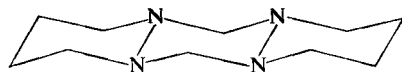
trans-1,2,3,4,5,6-Hexamethylhexahydro-1,2,4,5-tetrazine is shown by ^{13}C NMR to exist with both C—Me groups equatorial in the aeae conformation with some evidence for aaaa as a minor conformer.³⁷⁵

Some of these systems have been examined by X-ray analysis in the solid state.^{375a} When a single conformation was found to exist in solution, this is reflected in the crystal structure, as for the saturated tricyclic derivative **480** in the e_4 and the tetrabenzyl monocyclic **491** in the aeae conformation. The unsaturated tricyclic **479** crystallizes in the ae_3 unsymmetrical form, which is the largest component of the solution equilibrium. However, the 1,4-dimethyl-2,5-dibenzyl monocyclic derivative **486** crystallizes in the aeae conformation, which contributes only 33% to the solution equilibrium. 1,4-Dimethylhexahydro-1,2,4,5-tetrazine crystallizes with the *N*-methyl groups equatorial and the *N*-hydrogen atoms axial.³⁷⁶



Bond lengths	
N-1—N-2	1.452 Å
N-1—C-6	1.471 Å

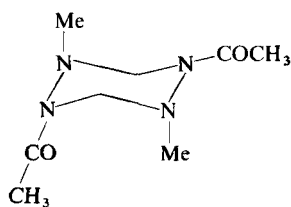
Bond angles	
N-4—C-3—N-2	110.3°
C-3—N-2—N-1	105.7°
N-2—N-1—C-6	112.3°



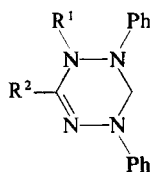
³⁷⁵ A. R. Katritzky, I. J. Ferguson, and R. C. Patel, *J. C. S. Perkin II*, 981 (1979).

^{375a} A. R. Katritzky, V. J. Baker, M. Camalli, R. Spagna, and A. Vacagio, *J. C. S. Perkin II*, 1733 (1980).

³⁷⁶ G. B. Ansell, J. L. Erickson, and D. W. Moore, *Chem. Commun.*, 446 (1970); *J. C. S. Perkin II*, 270 (1975).



(494)



(495)

Photoelectron spectroscopic measurements for four hexahydrotetrazines³⁴⁸ elucidate the vapor phase equilibria for (a) the tetrabenzyl derivative **491**, which exists as aeae, and (b) the hexamethyl compound **498**, which exists mainly as aeae. However, definite conclusions are not possible for the dimethyldibenzyl monocyclic **486** and the unsaturated tricyclic compounds **479**.

Evidence from vibrational spectroscopy and dipole moments is discussed in Ref. 374: in general, it is compatible with the other evidence, although this is not the case for the tetrabenzyl derivative.

The antisymmetric structure **494** has been proposed for the *N,N*-diacetyl-2,5-dimethyltetrazine.^{377,378} High energy barriers (Table XXXI) have been found for a variety of 1,2,3,4-tetrahydro-1,2,4,5-tetrazines (495).³⁷⁹

TABLE XXXI
INVERSION BARRIERS IN 2,4-DIPHENYL-1,2,3,4-
TETRAHYDRO-1,2,4,5-TETRAZINES³⁷⁹

Compound	ΔG_c^\ddagger (kcal mol ⁻¹)	<i>T</i> (°C)
495: R ¹ = CH ₂ Ph, R ² = H	12.4	-20
R ¹ = Me, R ² = <i>t</i> -Bu	14.3	+27
R ¹ = CH ₂ Ph, R ² = <i>t</i> -Bu	16.4	+59
R ¹ = <i>i</i> Pr, R ² = H	20.4	+145

5. Rationalization of Conformational Equilibria for Hexahydrotetrazines

If entropy considerations dominated, then conformations Y:Z:X:W (see Fig. 26) would coexist in the ratio 1:8:2:4.³⁷⁴ That W/Z is always large

³⁷⁷ S. Hammerum, *Acta Chem. Scand.* **27**, 779 (1973).

³⁷⁸ H. Dorn and H. Dölcher, *Justus Liebigs Ann. Chem.* **717**, 104 (1968).

³⁷⁹ F. A. Neugebauer and A. Mannschreck, *Tetrahedron* **28**, 2533 (1972).

(except for the tricyclic compounds where W cannot exist) must be due to a ΔH term caused by electronic as well as steric reasons. Electronically, a 1,3-diaxial lone-pair–lone-pair interaction present in Z is relieved in W, and, sterically, the ae conformation of Z is less favored than the aa of W. An electronic term α , similar to that just discussed, will favor X over Z and Z, in turn, over Y. However, an important steric term β can favor Y over Z, and, in turn, Z over X. The relative stabilities of the four conformations are represented in Fig. 26, and this enables the clarification and rationalization of the main features of the conformational equilibria in this series as follows.

(i) For the unsaturated tricyclic compound, the terms α and β approximately cancel; W cannot exist, but the other three conformations, X, Z, and Y, are all significantly populated.

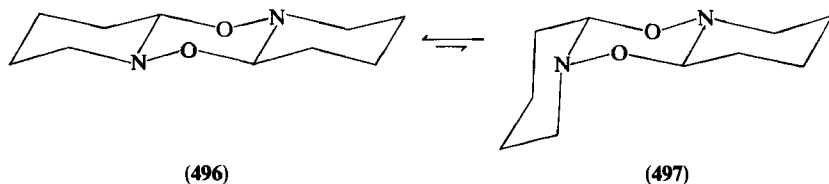
(ii) For the saturated tricyclic compound, the steric term is dominant and the net ΔH term favors Y, with Z unimportant and X very small indeed.

(iii) For the tetraisopropyl derivative, the steric term is again dominant; indeed, models show that severe interactions will prevent two adjacent isopropyl groups in the ae conformations. Hence this compound exists in sets I and III, and within set III, conformation W alone is significantly populated.

(iv) The monocyclic tetrazines investigated, apart from the tetraisopropyl derivative, all exist in conformations X and/or W. The balance is here a more subtle one, and it is not completely clear why the tetramethyl compound takes up conformation W, the tetrabenzyl derivative conformation X, whereas the tetraethyl- and the dibenzyl dimethyl derivatives occur as mixtures of X and W.

6. Perhydrodioxadiazines

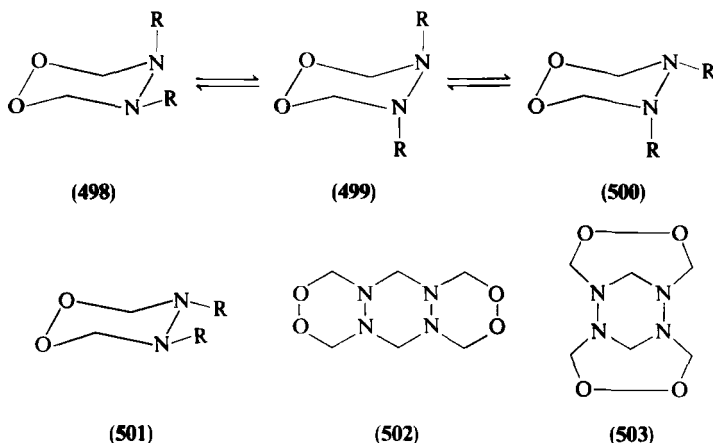
a. *Tetrahydro-1,4,2,5-dioxadiazines*. Perhydrodipyrido[1,2-b:1',2'-e]-1,4,2,5-dioxadiazine crystallizes in the trans-trans conformation **496**. In solution, the equilibrium **496** \rightleftharpoons **497** is shown by ^{13}C NMR to contain $\sim 10\%$ **497** at 25°C (ΔG^\ddagger_{80} for the minor conformation \rightarrow transition state, $12.7 \pm 0.4 \text{ kcal mol}^{-1}$).³⁸⁰ The trans-2,8-di-*tert*-butyl derivative of **496**, as expected,



³⁸⁰ A. R. Katritzky, R. Patel, S. Saba, R. L. Harlow, and S. H. Simonsen, *J. C. S. Perkin II*, 818 (1978).

adopts the trans-trans conformation, whereas the cis isomer adopts the conformation analogous to **497** rather than the alternative N-inside cis conformation.^{380a}

b. *Tetrahydro-1,2,4,5-dioxadiazines*. ¹H- and ¹³C-NMR spectra indicate that the 4,5-dimethyl and 4,5-diethyl derivatives exist very predominantly in the equilibrating ea and/or aa conformation **498** \rightleftharpoons **499** \rightleftharpoons **500**. For the diisopropyl analog, this set coexists with $\sim 20\%$ of the ee conformer **501**.³⁸¹ The tricyclic derivative originally thought³⁸¹ to have structure **502**, has been shown to be the 7:6:7 tricyclic derivative **503**.³⁸²



ACKNOWLEDGMENTS

We thank Drs. Ernest E. Eliel, Frank E. Riddell, and Michael J. T. Robinson for helpful comments on the manuscript.

^{380a} E. Gössinger, *Monatsh.* **113**, 339 (1982).

³⁸¹ A. R. Katritzky, V. J. Baker, F. M. S. Brito-Palma, J. M. Sullivan, and R. B. Finzel, *J. C. S. Perkin II*, 1133 (1979).

³⁸² S. N. Whittleton, P. Seiler, and J. D. Dunitz, *Helv. Chim. Acta* **64**, 2614 (1981).

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Applications of Phase Transfer Catalysis in Heterocyclic Chemistry

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I. Introduction

Phase transfer catalysis (PTC), or more generally, applications of two-phase systems, is one of the most important recent methodological developments in organic synthesis. It is important because it simplifies procedures, eliminates expensive, inconvenient, and dangerous reactants and solvents, and also allows one to perform many reactions that otherwise proceed unsatisfactory or do not proceed at all. PTC has been reviewed,¹⁻¹² but only one review concerns the chemistry of heterocyclic compounds.¹³

¹ E. V. Dehmlow and S. S. Dehmlow, "Phase Transfer Catalysis." Springer-Verlag, Berlin and New York, 1980.

² C. M. Starks and C. Liotta, "Phase Transfer Catalysis: Principles and Techniques." Academic Press, New York, 1978.

³ W. P. Weber and G. W. Gokel, "Phase Transfer Catalysis in Organic Synthesis." Springer-Verlag, Berlin and New York, 1977.

⁴ W. E. Keller, "Compendium of Phase Transfer Reactions." Fluka AG, Buchs, Switzerland.

⁵ M. Makosza, *Surv. Prog. Chem.* **9**, 1 (1980).

⁶ M. Makosza, *In Advances in Solution Chemistry* 11, (I. Bertini, L. Lunazzi, and A. Dei, eds.), p. 309. Plenum, New York, 1981.

⁷ G. W. Gokel and W. P. Weber, *J. Chem. Educ.* **55**, 350 (1978).

⁸ W. P. Weber and G. W. Gokel, *J. Chem. Educ.* **55**, 429 (1978).

⁹ J. Dockx, *Synthesis*, 441 (1973).

¹⁰ J. M. McIntosh, *J. Chem. Educ.* **55**, 235 (1978).

¹¹ M. Makosza, *Pure Appl. Chem.* **43**, 439 (1975).

¹² J. M. Lehn, *Acc. Chem. Res.* **11**, 49 (1978).

¹³ R. Gallo, H. Dou, and P. Hassanaly, *Bull. Soc. Chim. Belg.* **90**, 849 (1981).

A. GENERAL DEFINITIONS

In general, the term PTC describes the methodology for reactions of anionic species (inorganic, organic, and complex organometallic anions), based on the continuous formation of lipophilic ion pairs with lipophilic cations. Such ion pairs are soluble in nonpolar solvents. This approach becomes particularly advantageous when reactions are carried out in systems containing two immiscible phases: the organic phase where all reactions take place, and the inorganic phase (aqueous or solid anhydrous), which is the source of the anions or the base for their generation. The general principles of this technique and the concept behind it are better shown by two examples: cyanation of an alkyl chloride and addition of dichlorocarbene to an alkene.

An alkyl chloride (e.g., octyl chloride) does not form a nitrile when stirred with aqueous sodium cyanide because the reactants are located in different, immiscible phases. Addition of a small quantity (e.g., 1 mol %) of a lipophilic tetraalkyl ammonium salt ($R_4N^+Cl^-$ or Q^+Cl^-) results in the fast formation of the nitrile. Substitution occurs because the ammonium salt, which is dissolved in the organic phase, exchanges anions with the aqueous phase to form Q^+CN^- , which reacts rapidly with the alkyl chloride, forming the nitrile and Q^+Cl^- . Anion exchange again brings to the organic phase another CN^- ion. This continuous transfer of CN^- ions to the organic and Cl^- ions to the aqueous phase is due to the tetraalkyl ammonium salt acting as the transfer agent—phase transfer catalysis.

Generation of dichlorocarbene and its addition to an alkene in a two-phase system proceeds somewhat differently. Here a solution of an alkene in chloroform forms the organic phase; the other is concentrated aqueous NaOH. The first step, deprotonation of chloroform, occurs at the phase boundary; then the trichloromethyl anion formed at the phase boundary enters the organic phase in the form of ion pairs with Q^+ . Inside the organic phase the anions dissociate reversibly to dichlorocarbene and Q^+Cl^- exchanges anions at the phase boundary so that Cl^- passes into the aqueous phase and another trichloromethyl anion into the organic phase. Anions are transferred to the organic phase not from the aqueous phase but from the phase boundary. Reference 5 contains additional details.

Five approaches may be described:

1. Typical phase transfer catalysis in liquid-liquid systems combines processes in which Na^+ or K^+ salts of inorganic and organic anions derived from strong acids (phenolates, thiolates, carboxylates, etc.) are continuously transferred from aqueous (often alkaline) solutions to the organic phase by the phase transfer catalysts. Applications include nucleophilic substitution, addition, elimination, oxidation, and reduction reactions.

2. Reactions of carbanions, anions of weak organic acids (e.g., indole or carbazole), and dihalocarbenes may be carried out in liquid-liquid systems, in which concentrated aqueous sodium hydroxide is the aqueous phase. The term phase transfer catalysis is mechanistically incorrect; these are often referred to as catalytic two-phase systems. Numerous reactions of carbanions including alkylation, nitroarylation, addition, the Darzens condensation, cyclopropanation, and also a variety of reactions of dihalocarbenes are conveniently carried out in this way.

3. In solid-liquid systems anhydrous solid salts or bases form the inorganic phase. The phase transfer catalyst brings the required anions into the nonpolar medium by ion exchange with the solid phase or by solubilizing the salt. An appealing term "naked anions" is often used here. The system is recommended when traces of water should be avoided.

4. Ion-pair extraction, or extractive alkylation, is essentially identical to PTC in liquid-liquid systems, but the R_4N^+ salts are used in stoichiometric quantities. The intermediate R_4N^+ salts of the required anions can be prepared and isolated.¹⁴

5. Tri-phase catalysis refers to typical PTC in liquid-liquid systems with the phase transfer catalyst bound to polymeric insoluble supports.¹⁵⁻²⁰ These systems have attracted considerable attention because of the expectation of simple separation and reuse of the catalysts. Further quantitative data are needed.

B. CATALYSTS

The following is a list of abbreviations used for catalysts throughout the chapter.

Adogen 464:	methyltrialkylammonium bromide; alkyl groups are mixture of C_8 - C_{10} straight chains (average of nine carbons)
Aliquat 336:	technical grade methyltrioctylammonium chloride
CTEACl:	cetyltriethylammonium chloride
CTMAB:	cetyltrimethylammonium bromide
222-Cryptate:	diaza-1,10-hexaoxa-4,7,13,16,21,24-bicyclo[8.8.8]hexacosane

¹⁴ A. Brändström, "Preparative Ion Pair Extraction." Apotekarsocieteten, Stockholm, 1976.

¹⁵ For a review, see S. L. Regen, *Angew. Chem., Int. Ed. Engl.* **18**, 421 (1979).

¹⁶ S. L. Regen, *J. Am. Chem. Soc.* **98**, 6270 (1976).

¹⁷ S. L. Regen, *J. Am. Chem. Soc.* **99**, 3838 (1977).

¹⁸ S. L. Regen and L. Dulak, *J. Am. Chem. Soc.* **99**, 623 (1977).

¹⁹ H. Komeili-Zadeh, H. Dou, and J. Metzger, *J. Org. Chem.* **43**, 156 (1978).

²⁰ S. L. Regen, D. Bolikal, and C. Barcelon, *J. Org. Chem.* **46**, 2511 (1981).

DHP:	2,3-dihydro-4 <i>H</i> -pyran
PPTS:	pyridinium <i>p</i> -toluenesulfonate
PTC:	phase transfer catalysis
TBAB:	tetra- <i>n</i> -butylammonium bromide
TBACl or TBAC:	tetra- <i>n</i> -butylammonium chloride
TBAF:	tetra- <i>n</i> -butylammonium fluoride
TBAHSO ₄ :	tetra- <i>n</i> -butylammonium hydrogensulfate
TBAI:	tetra- <i>n</i> -butylammonium iodide
TEBA:	triethylbenzylammonium chloride

The catalysts must supply the system with lipophilic cations in order to form, with required anions, ion pairs able to enter nonpolar media. The most typical catalysts are tetraalkyl ammonium (TAA) salts $R_4N^+X^-$, particularly those having at least 16 carbon atoms in the four R groups. Similar lipophilic catalysts are tetraalkylphosphonium and -arsonium or trialkylsulfonium salts, which are less available and usually less stable. They are therefore of negligible practical use. There are a few reports on the use of trialkylamines as catalysts in some two-phase reactions. Usually these amines are quaternized by a reactant; actually these reactions are catalyzed by TAA salts. More complicated is the generation of dihalocarbenes with trialkylamines. The amines form, with the carbene, an ammonium ylide, which acts as a base in the organic phase.

Sodium or potassium ions can also participate in the phase-transfer process when they are converted to lipophilic cations by complexation or by strong specific solvation. A variety of neutral organic compounds are able to form reasonably stable complexes with K^+ or Na^+ and can act as catalysts in typical phase-transfer processes. Such compounds include monocyclic polyethers, or crown ethers (1), and bicyclic aminopolyethers (cryptates) (2). They can solubilize inorganic salts in nonpolar solvents and are particularly recommended for reactions of naked anions. Applications of these compounds have been studied.^{12,21-31}

²¹ J. M. Lehn, *Pure Appl. Chem.* **52**, 2303 (1980).

²² F. Vögtle and E. Weber, *Angew. Chem., Int. Ed. Engl.* **18**, 753 (1979).

²³ C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.* **11**, 16 (1972).

²⁴ G. W. Gokel and H. D. Durst, *Synthesis*, 168 (1976).

²⁵ J. J. Christensen, D. J. Etough, and R. M. Izatt, *Chem. Rev.* **74**, 351 (1974).

²⁶ J. M. Lehn, *Pure Appl. Chem.* **49**, 857 (1977).

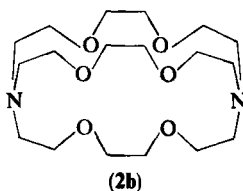
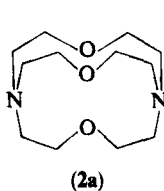
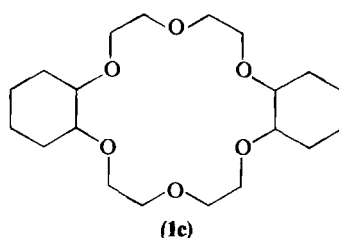
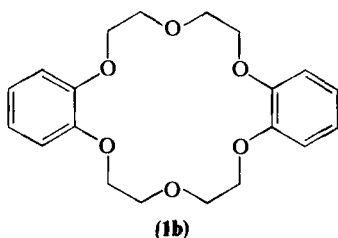
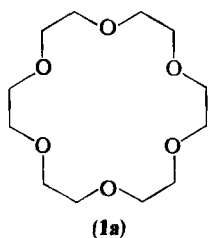
²⁷ J. M. Lehn, *Pure Appl. Chem.* **50**, 871 (1978).

²⁸ E. Weber and F. Vögtle, *Top. Curr. Chem.* **98**, 1 (1981).

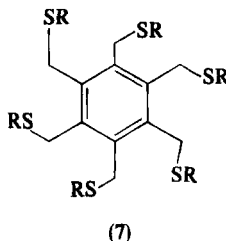
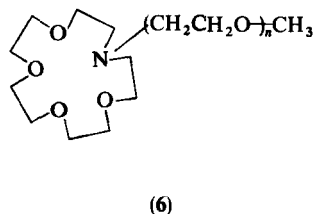
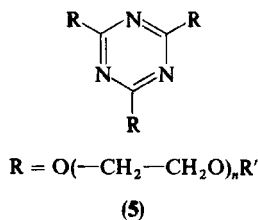
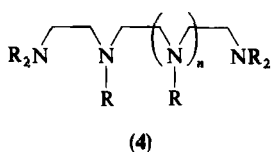
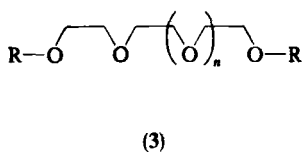
²⁹ F. De Jong and D. N. Reinhoudt, *Adv. Phys. Org. Chem.* **17**, 279 (1980).

³⁰ J. S. Bradshaw and P. E. Stott, *Tetrahedron* **36**, 461 (1980).

³¹ G. W. Gokel and S. H. Korzenowski, "Macrocyclic Polyethers Synthesis." Springer-Verlag, Berlin and New York, 1982.



Although acyclic polyethers, e.g., polyethylene glycols, form less stable solvates than the cyclic counterparts, they are also able to act as catalysts in biphasic systems. Typical structures of open-chain equivalents of crown ethers and cryptates are glymes³²⁻³⁴ (3); polyethylenamines^{35,36} (4); poly-podes^{37,38} (5); lariat ethers^{39,40} (6); and octopus⁴¹ (7).



³² H. Lehmkuhl, F. Rabet, and K. Hanschild, *Synthesis*, 184 (1977).

³³ D. G. Lee and V. S. Chang, *J. Org. Chem.* **43**, 1532 (1978).

³⁴ K. Yoshikagu and S. L. Regen, *J. Org. Chem.* **47**, 2493 (1982).

³⁵ H. Normant, T. Cuvigny, and P. Savignac, *Synthesis*, 805 (1975).

³⁶ S. Farhat, R. Gallo, and J. Metzger, *C.R. Acad. Sci., Ser. C* **287**, 581 (1978).

³⁷ M. Cinquini, F. Montanari, and P. Tundo, *J. C. S. Chem. Commun.*, 878 (1974).

³⁸ R. Fornasier and F. Montanari, *Tetrahedron Lett.*, 1381 (1976).

³⁹ D. M. Dishong, C. J. Diamond, and G. W. Gokel, *Tetrahedron Lett.*, 1663 (1981).

⁴⁰ R. A. Schultz, D. M. Dishong, and G. W. Gokel, *J. Am. Chem. Soc.* **104**, 625 (1982).

⁴¹ F. Vögtle and E. Weber, *Angew. Chem.* **86**, 896 (1974).

Because there is a large set of compounds able to act as catalysts, one needs guidelines for their selection. There are four main criteria: availability, lipophilicity of the ion-pair catalyst cation-reacting anion, stability of the cation, and separation of the product from the catalyst. TAA salts meet all these criteria. Readily available is a large range of cations from highly hydrophilic (Me_4N^+) to highly lipophilic (R_4N^+ with $\text{R} = \text{C}_5, \text{C}_6, \text{C}_7$, etc.), so that one can select a proper cation for a given reaction. The R_4N^+ ions are sufficiently stable in the presence of strong bases and nucleophiles up to 80–100°C, and they can be easily separated.

Crown ethers and cryptates are phase transfer catalysts but the use of these compounds in PTC reactions is limited to cases in which TAA salts are unsuitable.⁴²

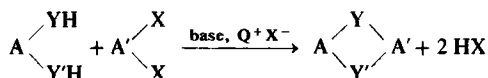
II. Heterocyclizations

The following syntheses of heterocyclic rings have been arranged according to the general scheme of heterocyclization and to the presumed reaction course in order to show general features.

A. ALIPHATIC NUCLEOPHILIC SUBSTITUTIONS

1. Two Nucleophilic Atoms and Two Leaving Groups

The general reaction scheme is the following:

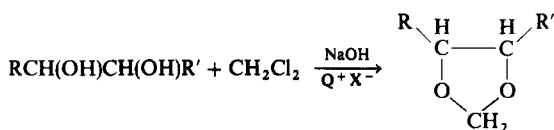


where Y or Y' = OH, SH, CS, NH, or CH, and X is a leaving group, mainly a halide (Cl or Br) or a tosylate. A and A' are suitable alkyl, aralkyl, or aryl groups. Most heterocycles formed according to this scheme are five- and six-membered rings. In all cases the nucleophilic substitutions are obviously consecutive.

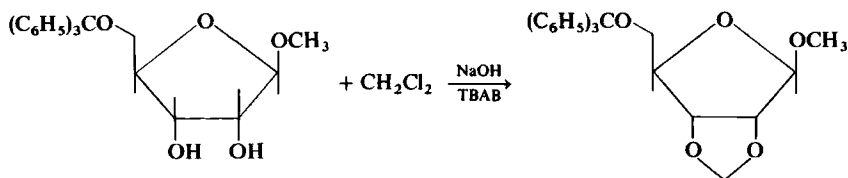
Gross and Dicesare⁴³ have described a preparation of cyclic acetals from vicinaldiols and methylene chloride using PTC. The method is of special interest in carbohydrate chemistry where these acetals are usually obtained under acidic conditions by the reaction of the diol with an aldehyde.

⁴² C. M. Starks, *CHEMTECH.*, 110 (1980).

⁴³ P. Dicesare and B. Gross, *Carbohydr. Res.* **48**, 271 (1976).

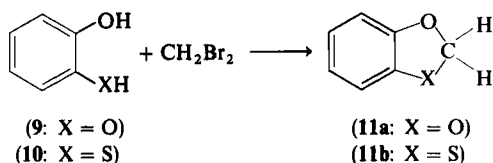


The phase transfer method has been also applied successfully, by Kim and Szarek,⁴⁴ to unreactive *trans*- β -diols and *cis*- β -diols (**8**).



Bashall and Collins⁴⁵ have treated catechol (**9**) with methylene dibromide under PTC conditions in the presence of Adogen. The 76% yield in this reaction is comparable to that obtained in DMSO,⁴⁶ but PTC is much more convenient. In DMSO, addition of pelleted sodium hydroxide and catechol is required in the absence of air.

Cabiddu *et al.*⁴⁷ have prepared 1,3-benzoxathiole (**11b**) from 2-hydroxy-benzenethiol (**10**). The yields are higher under biphasic conditions than those obtained using DMSO.



Merz⁴⁸ showed that reaction of benzoin with diethylene glycol ditosylate, in the presence of TBAB and of aqueous sodium hydroxide, yields 20% of crown ether **12**. This result, however, does not seem to be in agreement with the usual "template effect," achieved by complexation around a Na^+ or K^+ ion, as in the usual final step of crown ether syntheses.³⁰

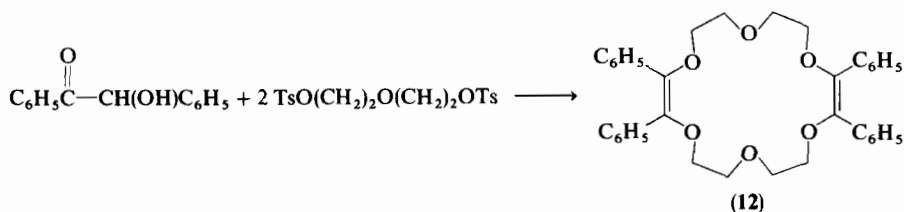
⁴⁴ K. S. Kim and W. A. Szarek, *Synthesis*, 48 (1978).

⁴⁵ A. P. Bashall and F. Collins, *Tetrahedron Lett.*, 3489 (1975).

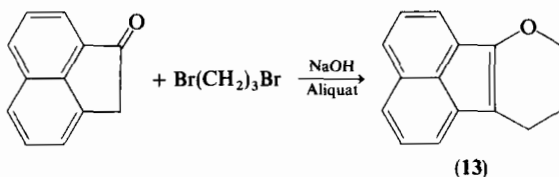
⁴⁶ W. Bonthron and J. W. Cornforth, *J. Chem. Soc. C*, 1202 (1969).

⁴⁷ S. Cabiddu, A. Maccioni, and M. Secci, *Synthesis*, 797 (1976).

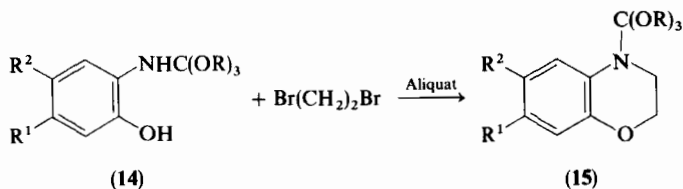
⁴⁸ A. Merz, *Angew. Chem., Int. Ed. Engl.* **16**, 467 (1977).



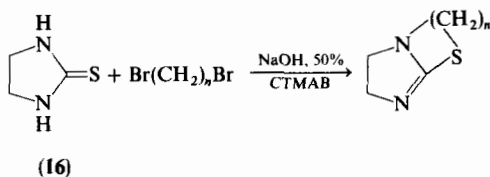
Jonczyk *et al.*⁴⁹ have reported reactions of cyclic enolates with 1,3-dibromopropane yielding dihydropyran **13**.



Coudert *et al.*⁵⁰ have prepared 1,4-benzoxazines (**15**) by the reaction of an *o*-acylaminophenol (**14**) with 1,2-dibromoethane, using solid NaOH and a mixture of CH_3CN and CH_2Cl_2 . Excellent yields are obtained when $\text{R}^3 = \text{phenyl}$; but the unsubstituted *o*-aminophenol did not undergo the reaction.



α,ω -Dibromo alkanes react with 2-thioxoimidazoline (**16**), 2-thioxoimidazole, or 2-thioxobenzimidazole, as reported by Dou *et al.*⁵¹ Aryl and benzo substituents increase the acidity of the NH and facilitate the conversion to the corresponding anion.

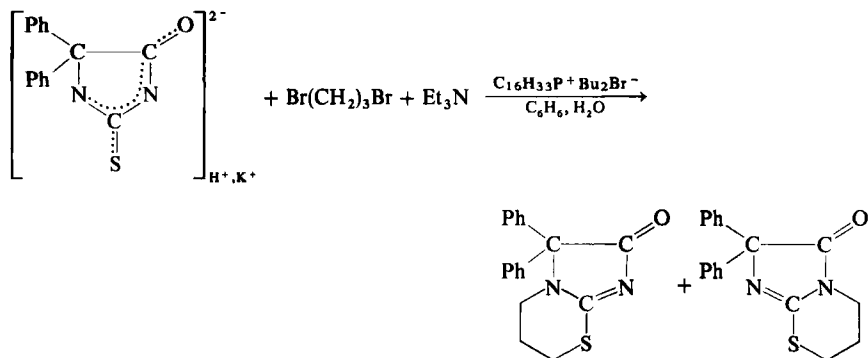


⁴⁹ A. Jonczyk, B. Serafin, and E. Skulimowska, *Rocz. Chem.* **45**, 1259 (1971).

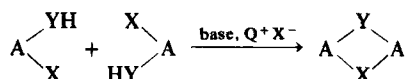
⁵⁰ G. Coudert, G. Guillaumet, and B. Loubinoux, *Synthesis*, 541 (1979).

⁵¹ H. Dou, M. Ludwikow, P. Hassanal, J. Kister, and J. Metzger, *J. Heterocycl. Chem.*, **17**, 393 (1980).

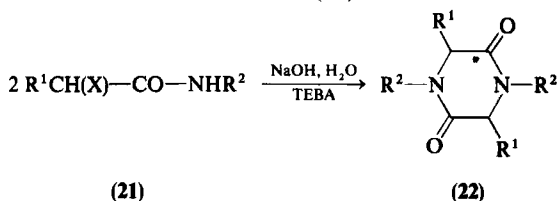
Derivatives of hydantoin, which has anticonvulsant activity, have been prepared by Mikolajczyk and co-workers,⁵² using PTC. The yield is almost quantitative. The selectivity is reversed, compared to the same reaction carried out in DME (dimethoxyethane).



Another general method of heterocyclization is that in which the nucleophile and the leaving group are attached to the same molecule.

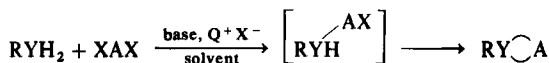


A reaction of this kind has recently been carried out by Okawara *et al.*^{53,54} who have reported an efficient synthesis of piperazine-2,5-diones (22) via PTC cyclization of α -halocarboxamides (21).



2. One Nucleophilic Atom and Two Leaving Groups

The general reaction scheme is the following:



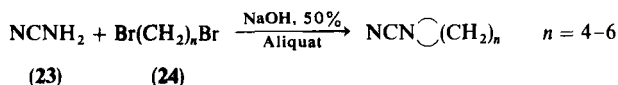
where Y is a nucleophilic atom, either N or C, and X a leaving group.

⁵² K. Kieckononowicz, A. Zejc, M. Mikolajczyk, A. Zaborski, J. Karolak, and M. W. Wieczorek, *Tetrahedron* **37**, 409 (1981).

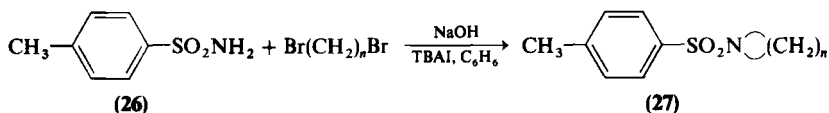
⁵³ T. Okawara, Y. Noguchi, T. Matsuda, and M. Furukawa, *Chem. Lett.* **2**, 185 (1981).

⁵⁴ T. Okawara, Y. Matsuda, and M. Furukawa, *Chem. Pharm. Bull.* **30**, 1225 (1982).

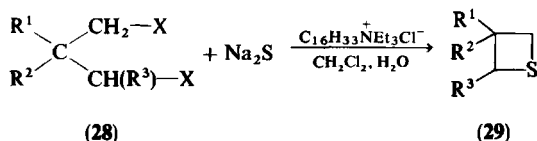
Primary amines RNH_2 cannot be converted to their anions, under PTC conditions, except if R is an electron-withdrawing substituent, such as CN or ArSO_2 . Thus cyanamide (23) has been alkylated, by Jonczyk *et al.*,⁵⁵ with α,ω -dihalogeno alkanes (24) or α,α' -dibromo-oxylenes to yield N-cyanopyrrolidine, N-cyano-piperidine, N-cyanohexahydroazepine, and 3-cyano-1,3-dihydroisoindole.



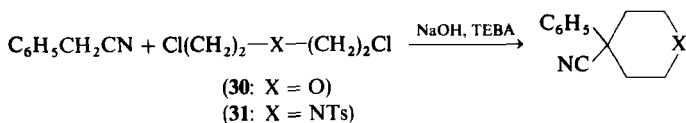
Isele *et al.*⁵⁶ have described recently the synthesis of *N*-tosylazacycloalkanes (**27**) by alkylation of *p*-toluenesulfonamide (**26**) with dihalogen alkanes under PTC conditions.

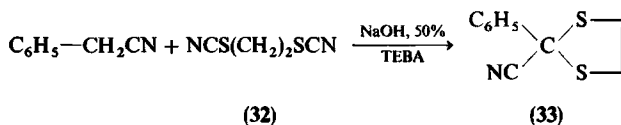


An efficient synthesis of thietanes (29) via reaction of 1,3-dihalo alkanes (28) with sodium sulfide was recently reported by Lancaster and Smith.⁵⁷



Phenylacetonitrile has been alkylated with di-(2-chloroethyl) ether (**30**) by Makosza and Serafin⁵⁸ and with 2,2'-dichlorodiethyltosylamine (**31**) by Rylski *et al.*⁵⁹

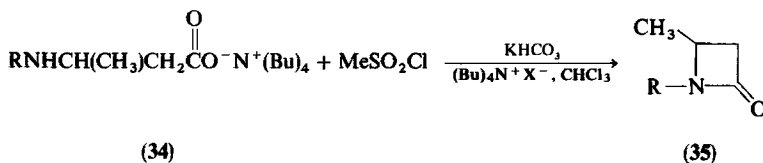




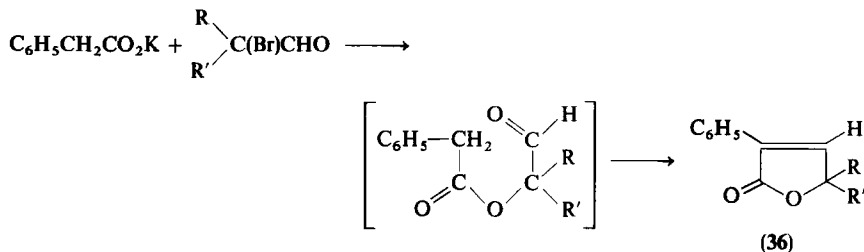
The results reported in this section are in agreement with the general behavior of intermolecular phase-transfer alkylations. The best yields are obtained when five- and six-membered rings are prepared.

B. CONSECUTIVE ADDITIONS AND/OR ALIPHATIC NUCLEOPHILIC SUBSTITUTIONS

A novel method for the synthesis of β -lactams (35), starting from β -amino acids (34) by means of a PT system, has been recently proposed by Watanabe and Mukaiyama.⁶¹ The reaction involves initial esterification of the carboxylic acid, which can later undergo the cyclization.



Padwa and Dehm⁶² have prepared furanones (36) by reaction of carboxylates with bromo aldehydes, catalyzed by 18-crown-6. The first step of the reaction is also an esterification of the potassium phenylacetate; the next step is equivalent to an intermolecular addition of a carbanion to an aldehyde, followed by elimination.

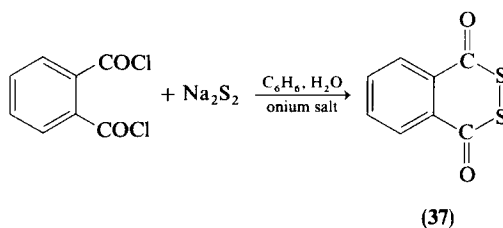


Bisacyl disulfides (37) have been conveniently prepared, using PTC, by Kodomari *et al.*⁶³

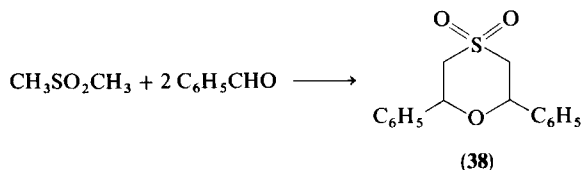
⁶¹ Y. Watanabe and T. Mukaiyama, *Chem. Lett.*, 443 (1981).

⁶² A. Pawda and D. Dehm, *J. Org. Chem.* **40**, 3139 (1975).

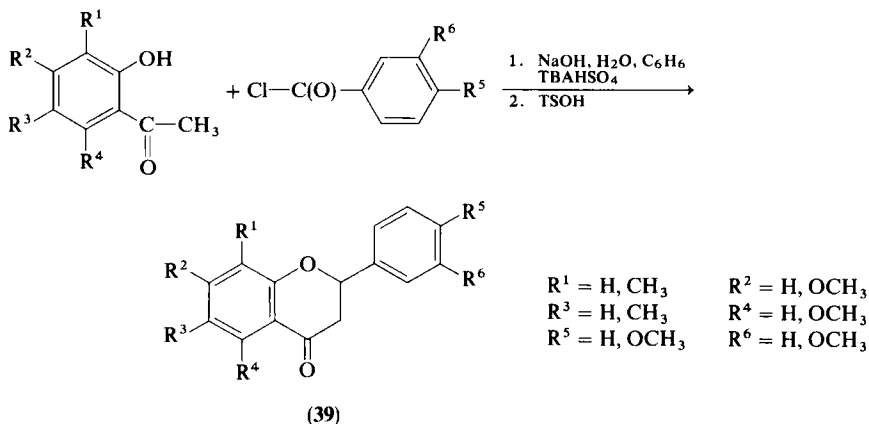
⁶³ M. Kodomari, M. Fukuda, and S. Yoshitani, *Synthesis* **8**, 637 (1981).



Condensation of dimethyl sulfone with benzaldehyde under PT conditions yields 3,5-diphenylthiadioxane *S,S*-dioxide (38). The product may be obtained in good yield, using TEBA or 18-crown-6.⁶⁴ Gokel⁶⁵ has shown that when the catalyst is a crown ether the reaction is complicated by the production of benzoic acid, presumably via a Cannizzaro reaction.



A facile Baker–Venkataraman synthesis of flavones (39), using PTC, has been recently proposed by Jain *et al.*⁶⁶

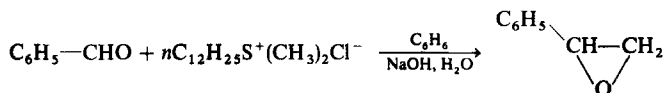


⁶⁴ G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.* **39**, 244 (1974).

⁶⁵ G. W. Gokel, H. W. Gerdes, and N. W. Rebert, *Tetrahedron Lett.*, 653 (1976).

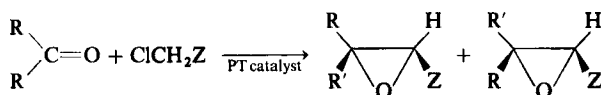
⁶⁶ P. K. Jain, J. K. Makrandi, and S. K. Grover, *Synthesis*, 221 (1982).

Phase transfer catalysis, or more correctly, two-phase systems, were widely applied in the synthesis of oxiranes via generation of sulfonium and sulfoxonium ylides and their subsequent reactions with carbonyl compounds.⁶⁷

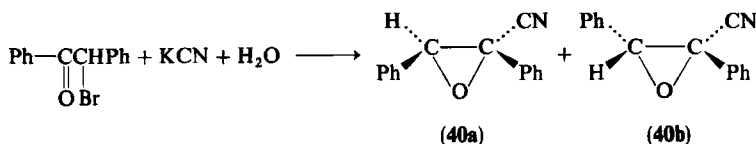


Many other examples^{68–71} are reported in the Fluka Compendium.⁴

Makosza and co-workers have reported the preparation of epoxides from α -halo carbanions and ketones, according to the Darzens reaction, under PT conditions, using TEBA^{72,73} or dibenzo-18-crown-6.⁷⁴ The ratio of isomers depends on the reaction conditions.^{75,76} Asymmetric induction has been reported in the Darzens reaction using chiral catalysts.^{77,78} The use of several chloro carbanions as well as K_2CO_3 and Na_2CO_3 in the solid state has also been studied.



Later Takahashi *et al.*⁷⁹ have reported an alternative synthesis of the cyanooxirane (**40a,b**) by carrying out the reaction between decyl bromide and potassium cyanide in the presence of quaternary ammonium catalysts. Compounds prepared by this method are similar to those obtained by the Darzens condensation with benzaldehyde in a two-phase system.⁷⁸



⁶⁷ Y. Yano, T. Okonogi, M. Sunaga, and W. Tagaki, *Chem. Commun.*, 527 (1973).

⁶⁸ A. Merz and G. Merkl, *Angew. Chem.* **85**, 867 (1973).

⁶⁹ T. Hiayama, T. Mishima, H. Sawada, and N. Nozaki, *J. Am. Chem. Soc.* **97**, 1626 (1975).

⁷⁰ M. J. Hatch, *J. Org. Chem.* **34**, 2133 (1969).

⁷¹ M. J. Farall, T. Durst, and J. M. Frechet, *Tetrahedron Lett.*, 203 (1979).

⁷² J. Jonczyk, M. Fedorynski, and M. Makosza, *Tetrahedron Lett.*, 2395 (1972).

⁷³ J. Golinsky and M. Makosza, *Synthesis*, 823 (1978).

⁷⁴ M. Makosza and M. Ludwikow, *Angew. Chem., Int. Ed. Engl.* **13**, 665 (1974).

⁷⁵ E. d'Incan and J. Seyden-Penne, *C.R. Acad. Sci., Ser. C* **281**, 1031 (1975).

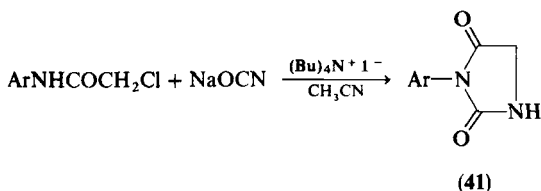
⁷⁶ A. Jonczyk, A. Kwast, and M. Makosza, *J. C. S. Chem. Commun.*, 902 (1977).

⁷⁷ J. C. Hummelen and H. Wynberg, *Tetrahedron Lett.*, 1089 (1978).

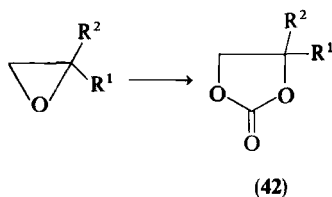
⁷⁸ S. Colonna, R. Fornasier, and U. Pfeiffer, *J. C. S. Perkin II*, 8 (1978).

⁷⁹ K. Takahashi, T. Nishizuka, and H. Lida, *Synth. Commun.*, 757 (1981).

Kim⁸⁰ reported recently a convenient synthesis of hydantoin derivatives (41) by PTC-catalyzed nucleophilic substitution, followed by cyclization.



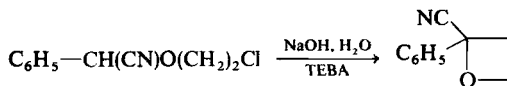
Naito *et al.*⁸¹ have reported that the addition of oxirane derivatives to CO_2 is catalyzed by potassium carboxylates or carbonates in the presence of a crown ether; cyclic carbonates (42) constitute the main product.



The last step of all the reactions described in the last two sections is a ring closure from a reactive intermediate that is formed in situ. In the next section are reported examples of ring closures that occur directly with the appropriate reagent under PT conditions.

C. RING-CLOSURE REACTIONS

Makosza and Goetzen⁸² have described the preparation of a four-membered ether by a method similar to that used for the alkylation of phenylacetonitrile and its derivatives.



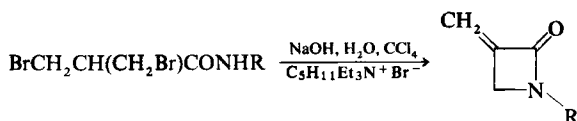
Fletcher and Kay⁸³ have obtained α -methylene- β -lactams in good yield from 3-bromo-2-bromomethylpropionamides by an internal N-alkylation of the amide, followed by elimination.

⁸⁰ S. C. Kim and B. M. Kwon, *Synthesis*, 795 (1982).

⁸¹ K. Naito, H. Koinuma, and H. Hirai, *Nippon Kagaku Kaishi*, 290 (1982).

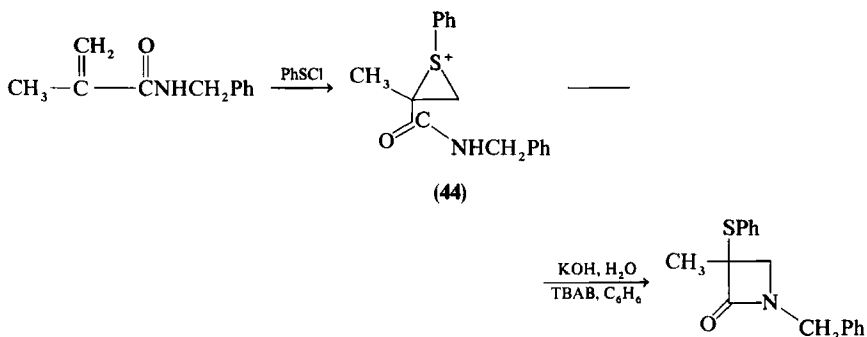
⁸² M. Makosza and T. Goetzen, *Rocz. Chem.* **46**, 1239 (1972).

⁸³ S. R. Fletcher and I. T. Kay, *J. C. S. Chem. Commun.*, 903 (1978).

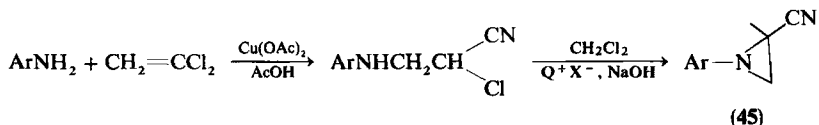


Takahata *et al.*^{84,85} have prepared monocyclic β -lactams in good yield by cyclizing $\text{BrCH}_2\text{CH}_2\text{CONHR}$ with solid KOH in CH_2Cl_2 in the presence of TBAB as a phase transfer catalyst.

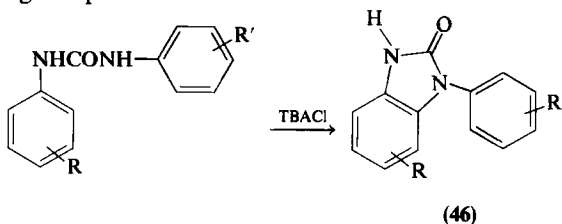
Ihara and Fukumoto⁸⁶ have reported a method of synthesis of β -lactams under PT conditions from a preformed cyclic sulfonium salt (44).



N-Acyl-2-cyanoaziridines have been prepared conveniently by Apparao *et al.*⁸⁷ in a two-step synthesis from *N*-aryl-2-cyanoaziridine (45). The intermediate step is a ring closure carried out under PTC conditions.



1-Arylbenzimidazolinones (46) have been prepared by cyclization of carbanilides, using a biphasic medium.⁸⁸



⁸⁴ H. Takahata, Y. Ohnishi, and T. Yamazaki, *Heterocycles* **14**, 467 (1980).

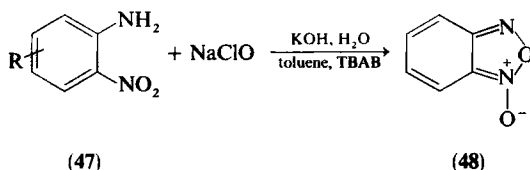
⁸⁵ H. Takahata, Y. Ohnishi, and T. Yamazaki, *Chem. Pharm. Bull.* **29**, 1063 (1981).

⁸⁶ M. Ihara and K. Fukumoto, *Heterocycles* **19**, 1435 (1982).

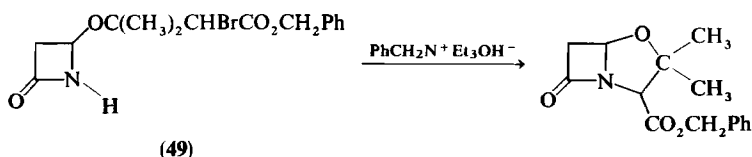
⁸⁷ S. Apparao, A. Kumar, H. Ila, and H. Junppa, *Synthesis*, 623 (1981).

⁸⁸ Dow Chemical Cie, British Patent 1,576,386 (1980).

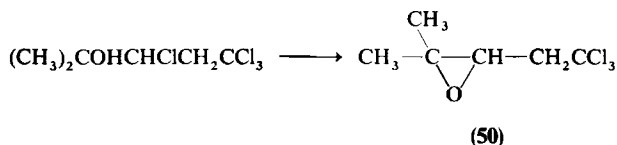
Fah⁸⁹ has patented a mild method, avoiding the risk of explosion, for converting *o*-nitroaniline derivatives (47) to benzofurane 1-oxides (48).



An alkoxyazetidinone (49) has been cyclized in a reaction that corresponds to an intramolecular lactam alkylation by Howarth and co-workers.⁹⁰

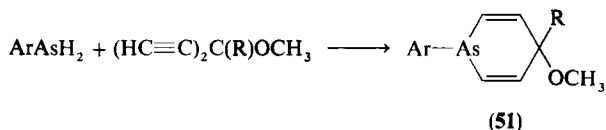


A halogenoalkyloxirane (50) has been prepared by an internal Williamson synthesis using TBACl.⁹¹



D. MISCELLANEOUS HETEROCYCLIZATION REACTIONS

Märkl *et al.*⁹² have obtained heterocyclohexa-2,5-dienes (51), by cycloaddition of arylphosphines, arylarsines, and dialkylstannanes with acetylene derivatives in the presence of 18-crown-6 and benzene. The technique is superior to the conventional free radical method (benzene, AIBN) or to the method employing a strong base (BuLi, THF, or $\text{NH}_2\text{Na}, \text{NH}_3$).



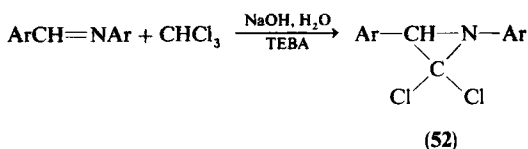
⁸⁹ H. Fah, U.S. Patent 4,185,018 (1980), to Ciba Geigy.

⁹⁰ A. G. Brown, D. F. Corbett, and T. T. Howarth, *J. C. S. Chem. Commun.*, 359 (1977).

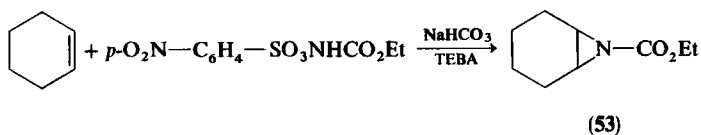
⁹¹ L. Toke, I. Bitter, R. Soos, I. Szekely, G. Kormoczi, Z. Bende, and A. Karpati, *Hung. Teljos* 19,381 (1981).

⁹² G. Märkl, H. Baier, and R. Liebl, *Synthesis*, 842 (1977).

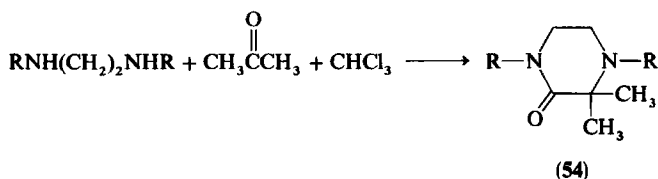
Addition of the PTC-generated dichlorocarbene to a variety of imines offers an efficient route to dichloroaziridine derivatives (52).^{93,94}



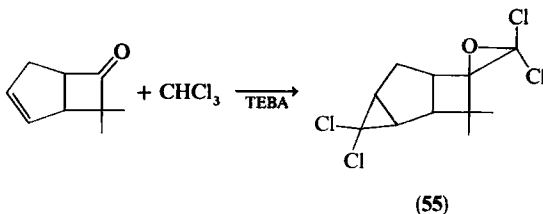
Carbethoxynitrene can also be generated under PT conditions; addition to alkenes gives aziridines (53).⁹⁵



Lai⁹⁶⁻⁹⁹ has reported a general method of preparation of substituted piperazinones (54) via reactions of ketones and haloform in the presence of quaternary ammonium catalysts.



Bellus and co-workers¹⁰⁰ have obtained relatively stable dichlorooxiranes (55) by reaction of chloroform with a sterically hindered carbonyl group.



⁹³ D. J. Sikkema, E. Molenaar, and D. B. van Buldenar, *Rec. Trav. Chim. Pays-Bas* **95**, 154 (1976).

⁹⁴ M. Makosza and A. Kacprowicz, *Rocz. Chem.* **48**, 2129 (1974).

⁹⁵ M. Seno, T. Namba, and H. Kise, *J. Org. Chem.* **43**, 3345 (1978).

⁹⁶ J. T. Lai, U.S. Patent 4,297,497 (1981), to Goodrich Cie.

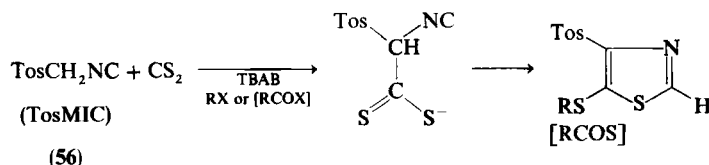
⁹⁷ J. T. Lai, *J. Org. Chem.* **45**, 754 (1980).

⁹⁸ J. T. Lai, *Synthesis*, 40 (1981).

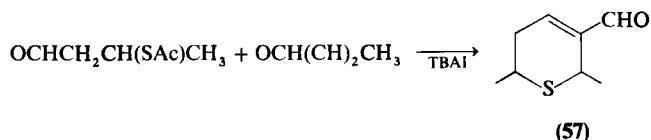
⁹⁹ J. T. Lai, *Synthesis*, 71 (1982).

¹⁰⁰ H. Greuter, T. Winkler, and D. Bellus, *Helv. Chim. Acta* **62**, 1275 (1979).

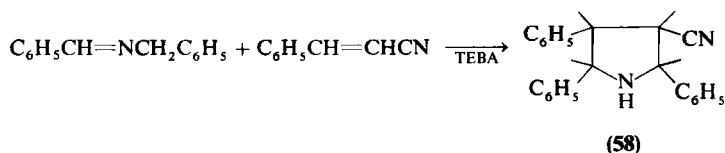
Van Leusen and Wildeman¹⁰¹ have realized a 1,3-thiazole synthesis, using the reagent TosMIC (tosylmethyl isocyanate) (56)¹⁰² and CS₂.



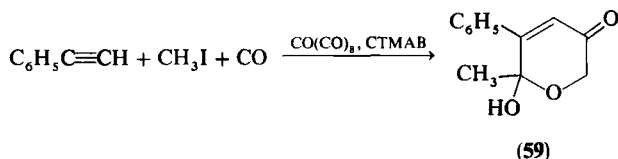
McIntosh and Khalil¹⁰³ have condensed 3-thioacetoxybutanal with acrolein under PT conditions to yield 5-thiacyclohexanecarboxaldehyde (57).



Dryanska *et al.*¹⁰⁴ have prepared pyrroles (58) by reaction of cinnamionitrile with *N*-benzylidenebenzylamine in the presence of a solvent.



A regiospecific synthesis of hydroxybutenolides (59) has been carried out by Alper *et al.*,¹⁰⁵ using cobalt carbonyl-catalyzed carbonylation of alkynes. More such examples of PTC in organometallic chemistry^{106–108} undoubtedly will be developed.



¹⁰¹ M. Van Leusen and J. Wildeman, *Synthesis*, 501 (1977).

¹⁰² M. Van Leusen, *Lect. Heterocycl. Chem.* **S111**, 5 (1980), Suppl. Issue of *J. Heterocycl. Chem.* **17**.

¹⁰³ J. M. McIntosh and H. Khalil, *J. Org. Chem.* **42**, 2123 (1977).

¹⁰⁴ V. Dryanska, K. Popandova, and C. Ivanov, *Tetrahedron Lett.*, 443 (1979).

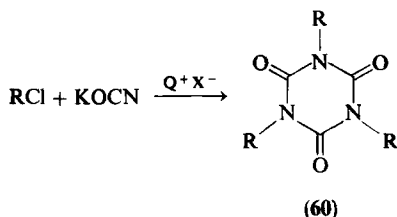
¹⁰⁵ H. Alper, J. K. Currie, and H. des Abbayes, *J. C. S. Chem. Commun.*, 311 (1978).

¹⁰⁶ L. Cassar, in "Fundamental Research in Homogeneous Catalysis" (M. Tsutsui and R. Ugo, eds.), Plenum, New York, 1977.

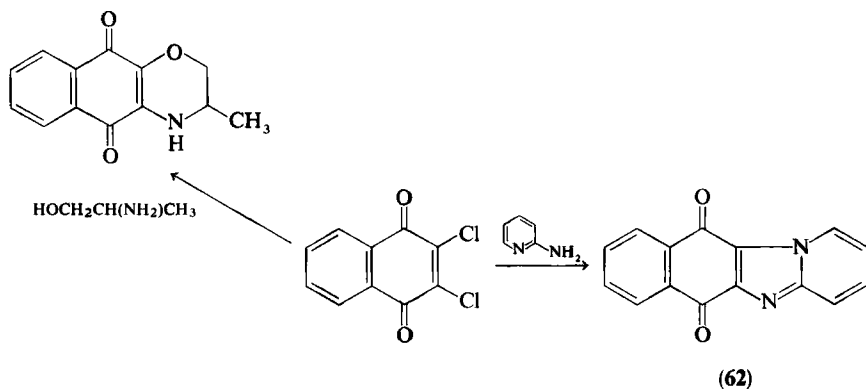
¹⁰⁷ H. Alper, *Adv. Organomet. Chem.* **19**, 183 (1981).

¹⁰⁸ L. Cassar, *Ann. N.Y. Acad. Sci.* **333**, 208 (1980).

Triazines (60) have been prepared by reaction of KOCN with an alkyl chloride, involving trimerization of alkyl isocyanate intermediates formed in solid-liquid PTC.¹⁰⁹



Al Shafei *et al.*¹¹⁰ have conveniently prepared several fused naphthoquinone derivatives by condensing ambident compounds, having N—N, N—O, or N—S nucleophilic centers, with 2,3-dichloronaphthoquinones (62), under PT conditions.



In the PTC system just considered, the concentration of the catalyst, usually does not exceed 2–5 mol % of the reagents. The concentration of the reactive intermediates cannot exceed that of the catalyst. Therefore, the PTC conditions mimic those of the high-dilution technique and are particularly favorable for cyclization reactions. Regen has described a macrolide synthesis¹¹¹ using the synergistic coupling of triphase catalysis and of “pseudodilution” characteristic of cross-linked polymers. A series of lactones was prepared in good yield under mild conditions without the use of conventional high-dilution techniques or of more sophisticated reagents.^{112,113}

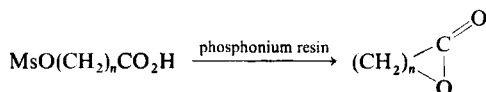
¹⁰⁹ K. F. Zenner and H. Appel, Ger. Offen. 2,126,296 (1972).

¹¹⁰ A. K. Elshafei, A. Sultan, and G. Vernin, *Heterocycles* **19**, 333 (1982).

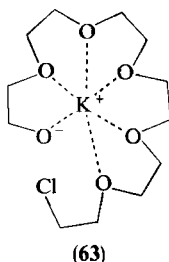
¹¹¹ S. L. Regen and Y. Kimura, *J. Am. Chem. Soc.* **104**, 2064 (1982).

¹¹² W. H. Kruizinga and R. M. Kellog, *J. Am. Chem. Soc.* **103**, 5183 (1981).

¹¹³ E. J. Corey and K. J. Nicolaou, *J. Am. Chem. Soc.* **96**, 5614 (1974).



Liquid-liquid PTC would seem to be convenient for the synthesis of crown ethers and derivatives. But most still use conventional conditions,^{28,29} probably because the synthesis of macrocyclic crown ethers gives better results when Na^+ or K^+ ions are involved. These ions can induce a "template effect" with the polyethyleneoxy chain **63**.



III. Modifications of Substituents on Heterocyclic Compounds

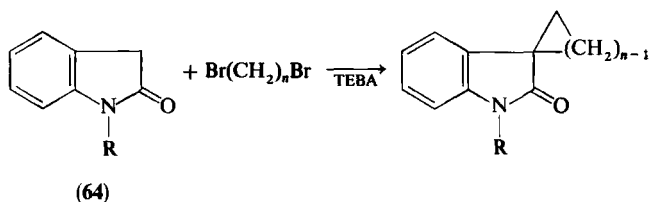
Most of the processes described in this section correspond to reactions in which the heterocycle behaves as a nucleophile. For the sake of clarity we have separated reactions in which the nucleophilic atom forms a part of the heterocyclic ring from those in which it is directly bonded to the heterocyclic ring. In some cases, however, heterocyclic molecules behave as ambident compounds, reacting at two or even more positions. PTC conditions are very favorable because the regioselectivity of the ambident anions is better controlled.

A. HETEROCYCLIC NUCLEOPHILES (REACTIVE ATOM IN THE RING)

1. C-Alkylations and C-Arylations

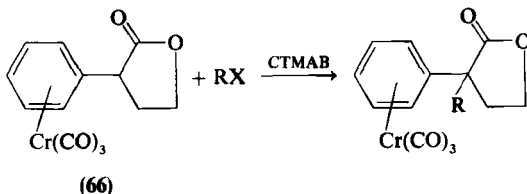
Oxindol (**64**) reacts at position 3 to give dialkylation with 2 mol of alkyl halide and a cycloaddition with an α,ω -dihalide.¹¹⁴

¹¹⁴ M. Makosza and M. Fedorynski, *Rocz. Chem.* **45**, 1861 (1971).



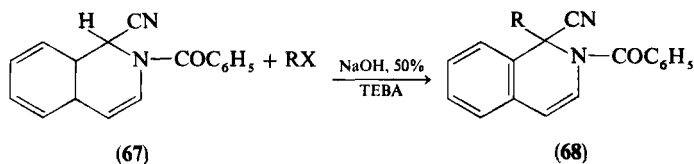
Makosza *et al.*¹¹⁵ have also reported similar reactions with a 3-substituted oxindol and an aryl halide. The reaction occurs only if the aryl halide is activated by an electron-withdrawing substituent.

des Abbayes and Boudeville¹¹⁶ have alkylated arylbutyrolactones in the presence of aqueous NaOH without evidence of significant hydrolysis of the lactone. Chromium tricarbonyl (**66**) served as a temporary complexing group of the aromatic ring.



The electron-withdrawing character of $\text{Cr}(\text{CO})_3$ can be used to promote the displacement of leaving groups on nonactivated aromatic rings in $\text{S}_{\text{N}}\text{Ar}$ reactions.¹¹⁷ Perhaps other $\text{S}_{\text{N}}\text{Ar}$ reactions can be run, taking advantage of $\text{Cr}(\text{CO})_3$ and of PTC activation.^{117a}

Makosza¹¹⁸ has also shown that Reissert compounds, *N*-benzoyl-1,2-dihydroisoquinaldenitrile (**67**), can be alkylated in the presence of NaOH and TEBA. Alkaline hydrolysis of alkylated **68** will give isoquinoline derivatives, which are starting materials for the synthesis of alkaloids.



¹¹⁵ M. Makosza, K. Wojciechowski, and M. Jawdosiuk, *Pol. J. Chem.* **52**, 1173 (1978).

¹¹⁶ H. des Abbayes and M. A. Boudeville, *J. Org. Chem.* **42**, 4104 (1977).

¹¹⁷ M. F. Semmelhack, H. T. Hall, M. Yoshifuji, and G. Clark, *J. Am. Chem. Soc.* **97**, 1247 (1975).

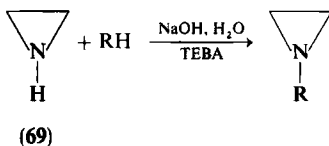
^{117a} An example of $\text{Cr}(\text{CO})_3$ and PTC activation was described after submission of this manuscript: A. Alemagna, P. del Buttero, C. Gorini, D. Landini, E. Licandro, and S. Maiorana, *J. Org. Chem.* **48**, 605 (1983).

¹¹⁸ M. Makosza, *Tetrahedron Lett.*, 677 (1969).

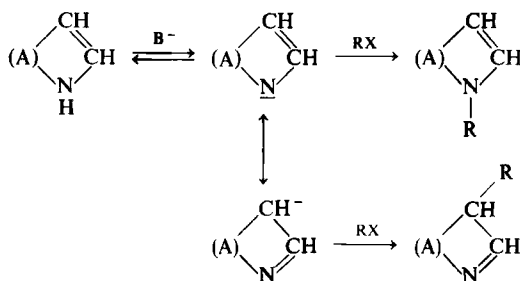
The insertions of PTC-generated dichlorocarbene into CH bonds of 1,3-dioxane and 1,3-dioxolane rings represent examples of C-alkylation of heterocyclic nucleophiles.^{119,120} The mechanism is different from those just considered because a carbanion on the heterocyclic ring probably is not formed during insertion.

2. *N*-Alkylations and *N*-Sulfonations

a. *Heterocyclic Compounds with One Nitrogen Atom.* Aziridines, **69** cannot be easily alkylated under conventional conditions because of rapid decomposition to open chain compounds. Lattes and co-workers¹²¹ showed that alkylation of aziridine can be carried out quantitatively under PT conditions.



A general problem in alkylation of nitrogen heterocycles is the regiochemistry of the corresponding anions. The ratio of *N*- versus *C*-alkylation usually depends on reaction conditions; PTC strongly favors *N*-alkylation.



For example, during *N*-alkylation of pyrrole under conventional alkaline conditions *C*-alkylation also occurs at positions 2 and 3. Thus the Grignard derivative of pyrrole¹²² reacting with dimethyl sulfate in HMPA gives a mixture of mono- and dimethylation products. The first example of pyrrole benzylation under PT conditions was reported by Jonczyk and Makosza.¹²³ The *N*-benzyl compound was the major product.

¹¹⁹ K. Steinbeck, *Chem. Ber.* **112**, 2402 (1979).

¹²⁰ K. Steinbeck, *Tetrahedron Lett.*, 2149 (1980).

¹²¹ M. Maurette, A. Lopez, R. Martino, and A. Lattes, *C.R. Acad. Sci., Ser. C* **282**, 599 (1976).

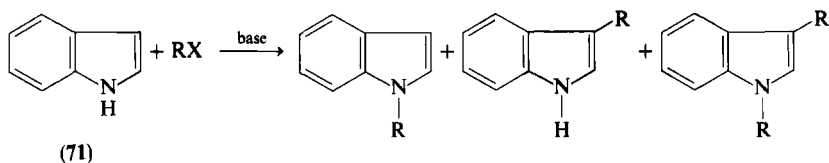
¹²² N. C. Wang, K. E. Teo, and H. J. Anderson, *Can. J. Chem.* **55**, 4112 (1977).

¹²³ A. Jonczyk and M. Makosza, *Rocz. Chem.* **49**, 1203 (1975).

Wang *et al.*¹²² have described methylation and alkylation of pyrrole and obtained mono-N-alkylation products with yields of 30–85%. An increase in the ratio of N- versus C-alkylation of pyrrole (and of other heterocyclic compounds bearing an acidic hydrogen atom) has been observed by Guida and Mathre,¹²⁴ who carried out the reaction with *t*-BuOK, 18-crown-6 (10%), and diethyl ether.

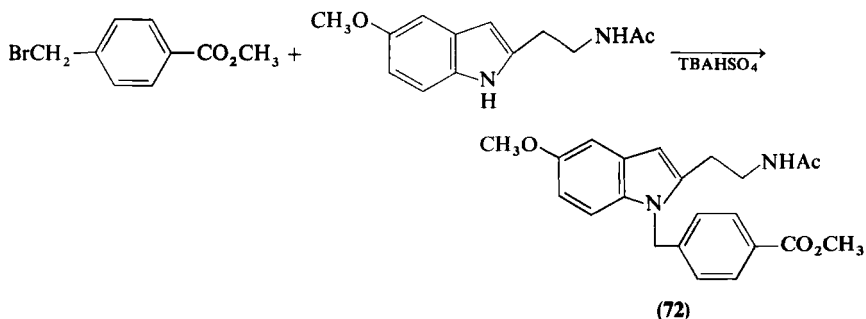
With benzyl, allyl, and primary alkyl halides the yields are 72–90%; they are low with isopropyl iodide (34%); with *tert*-butyl bromide no reaction occurred. This behavior is consistent with results already reported. Alkylation of anions often give poor results with secondary alkyl halides and no alkylation with tertiary alkyl halides.

Santaniello *et al.*¹²⁵ have N-alkylated pyrrole and indole (71) in the presence of crown-ether catalysts. The indolyl anion also behaves as an ambident nucleophile; alkylation occurs at nitrogen and at C-3.¹²⁶



Barco *et al.*¹²⁷ and Bocchi *et al.*¹²⁸ have described independently N-alkylation of indole in very good yield when primary halides or sulfates are used. With allyl halides,¹²⁸ however, alkylation occurs to a large extent at position 3.

More complicated examples of N-alkylation of indoles were reported by De Silva and Snieckus,¹²⁹ who have prepared intermediates of substituted tryptamines (72) by this method.



¹²⁴ W. C. Guida and D. J. Mathre, *J. Org. Chem.* **45**, 3172 (1980).

¹²⁵ E. Santaniello, C. Farachi, and F. Ponti, *Synthesis*, 617 (1979).

¹²⁶ J. Sundberg, "The Chemistry of Indoles." Academic Press, New York, 1970.

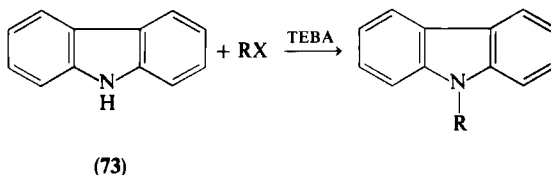
¹²⁷ A. Barco, S. Benetti, G. Pollini, and P. Bataldi, *Synthesis*, 124 (1976).

¹²⁸ V. Bocchi, G. Casnati, A. Dossena, and G. Villani, *Synthesis*, 414 (1976).

¹²⁹ S. O. De Silva and V. Snieckus, *Can. J. Chem.* **56**, 1621 (1978).

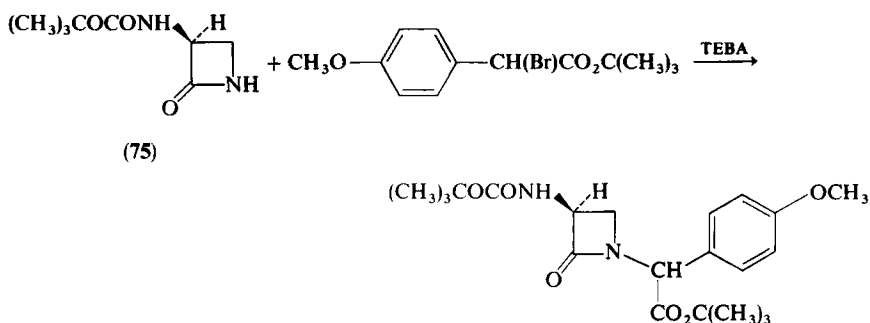
Illi¹³⁰ extended the work of Bocchi *et al.*¹²⁸ to the N-sulfonylation of indole: a method that could be used as well with other nitrogen heterocycles described in this section.

Carbazole (73) has also been alkylated by De Silva and Snieckus,¹²⁹ and later by Nishi *et al.*¹³¹

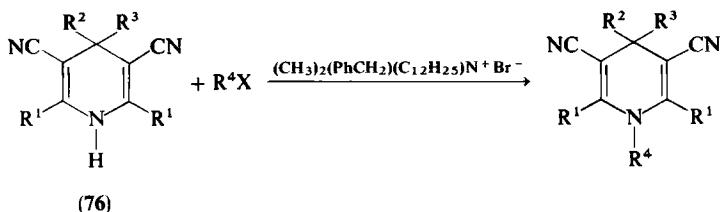


Phase transfer catalysis conditions have also been applied to the N-alkylation of lactams.¹³²⁻¹³⁴

Recently Mattingly and Miller¹³⁵ have described an alkylation of β -lactam 75 as a step in the synthesis of nocardicin.



1,4-Dihydropyridine derivatives (76) have been alkylated under PT conditions by Palecek and Kuthan¹³⁶ in good yield.



¹³⁰ V. O. Illi, *Synthesis*, 136 (1979).

¹³¹ H. Nishi, H. Kohno, and T. Kano, *Bull. Chem. Soc. Jpn.* **54**, 1897 (1981).

¹³² J. Palecek and J. Kuthan, *Z. Chem.* **17**, 260 (1977).

¹³³ R. Reuschlig, H. Pietsch, and A. Linkies, *Tetrahedron Lett.*, 615 (1978).

¹³⁴ H. Takahata, T. Hashizume, and T. Yamazaki, *Heterocycles* **12**, 1449 (1979).

¹³⁵ P. G. Mattingly and M. J. Miller, *J. Org. Chem.* **46**, 1557 (1981).

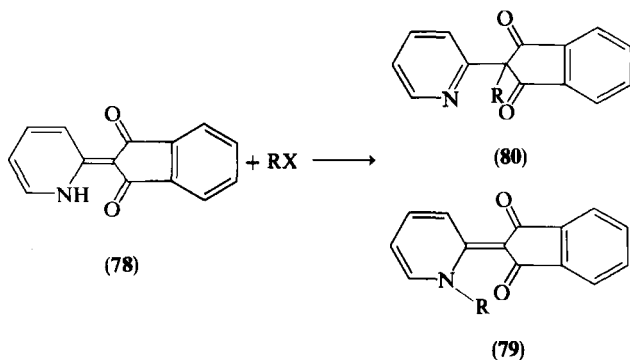
¹³⁶ J. Palecek and J. Kuthan, *Synthesis*, 550 (1976).

Alkylation of hydroxypyridines¹³⁷ has been studied under PT conditions. The results depend on the position of the hydroxy group and on the nature of the experimental conditions. 2- And 4-pyridone are alkylated at both nitrogen and oxygen with a little preference for nitrogen.¹³⁸ 3-Hydroxypyridine and 2-amino-3-hydroxypyridine¹³⁹ (see next section) give only O-alkylation.

Alkylation of substituted 4-hydroxyquinolines in a PTC system has been studied by Renault *et al.*¹⁴⁰ (see next section).

Masse¹⁴¹ obtained good yields on N-alkylating 2-chlorophenothiazine, using a biphasic system and TEBA as catalyst. When unreactive halides were used, a by-product was formed due to benzylation by the catalyst TEBA. This observation has been confirmed and clarified in a study of the behavior and stability of bi- and triphase transfer catalysts.¹⁴² Under the same conditions unsubstituted phenothiazine is not alkylated,¹⁴³ indicating an activating effect of the chloro substituent.

Le Baut and co-workers¹⁴⁴ have recently studied the alkylation of γ -pyronaphthalone (**78**) in order to increase the regioselectivity of reaction at the nitrogen atom of **79**. The results are good examples of increases in yield and selectivity, using PTC as compared to more conventional methods using nonpolar or polar aprotic solvents.



Thus the classic methods of preparation of **79**, using nonpolar solvents, give low yields and a mixture of **79** and **80**. The method using polar aprotic

¹³⁷ A. R. Stein and S. H. Tan, *Can. J. Chem.* **52**, 4050 (1974).

¹³⁸ H. Dou, P. Hassanaly, and J. Metzger, *J. Heterocycl. Chem.* **14**, 321 (1977).

¹³⁹ J. A. Bristol, I. Gross, and R. G. Lowey, *Synthesis*, 971 (1981).

¹⁴⁰ J. Renault, P. Mailliet, J. Berlot, and S. Renault, *C. R. Acad. Sci., Ser. C* **285**, 199 (1977).

¹⁴¹ J. Masse, *Synthesis*, 341 (1977).

¹⁴² H. Dou, R. Gallo, P. Hassanaly, and J. Metzger, *J. Org. Chem.* **42**, 4275 (1977).

¹⁴³ P. Cocagne, unpublished results.

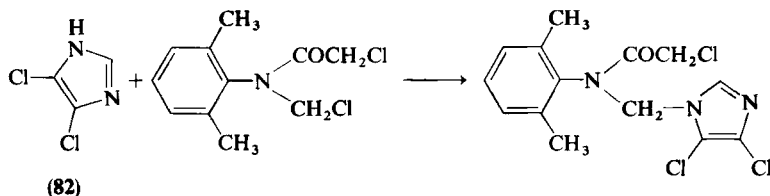
¹⁴⁴ R. C. Floch, D. G. Leblois, G. Y. Le Baut, P. C. Cadiot, J. Ploquin, and C. J. Clairc, *J. Chem. Res., Synop.*, 318 (1981).

solvents (DMF, NaH) gives a higher yield but the same selectivity. With the PT method (NaOH, CH_2Cl_2 , $\text{C}_{16}\text{H}_{33}\text{NMe}_3^+\text{Br}^-$) yields are even higher and only 1–5% of **80** is obtained.

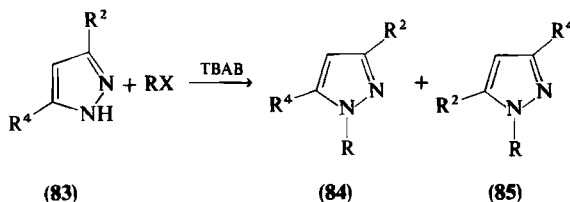
b. Heterocyclic Compounds with Two Nitrogen Atoms. Heterocycles with two nitrogen atoms have been selectively N-alkylated. The first study of imidazole and pyrazole alkylation has been reported by Dou and Metzger.^{144a}

Further examples of alkylation of imidazole derivatives were recently reported by Galous *et al.*¹⁴⁵ The nature and importance of significant factors in phase transfer alkylation of pyrazole was studied by Elguero *et al.*¹⁴⁶ Their conclusions are equivalent to those of Dehmloew and Lissel.¹⁴⁷ The optimization method used by Elguero *et al.* (several parameters at a time) is different from the conventional procedure (one parameter at a time) and will probably find applications in the future for optimization of organic syntheses.

Later, specific examples of alkylation of dichloro-4,5-imidazole (**82**) have been described by Eichen *et al.*¹⁴⁸



Tarrago *et al.*¹⁴⁹ have reported an interesting example of a change in selectivity induced by PT catalysis. In N-alkylation of pyrazoles (**83**), the ratio **84/85** is different under neutral or alkaline conditions, especially when a heteroatom with a lone pair is located ortho to one of the nitrogens of the ring.



^{144a} H. Dou and J. Metzger, *Bull. Soc. Chim. Fr.*, 1861 (1976).

¹⁴⁵ H. Galous, I. Bergerat, C. C. Farnoux, and M. Miocque, *Synthesis*, 1103 (1982).

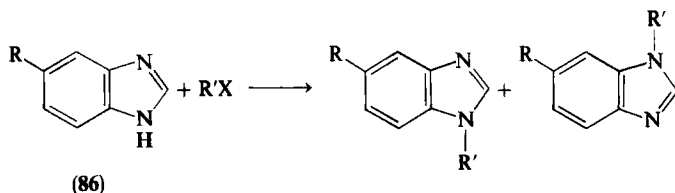
¹⁴⁶ J. Elguero, M. Espada, D. Mathieu, and R. Phan Tan Luu, *Ann. Quim.* **75**, 729 (1979).

¹⁴⁷ E. V. Dehmloew and M. Lissel, *J. Chem. Res., Synop.*, 310 (1978).

¹⁴⁸ K. Eichen, W. Rohr, and F. Linhart, *Ger. Offen.* 2,830,764 (1980), to BASF.

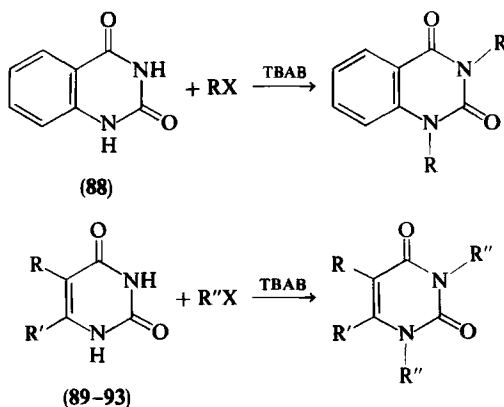
¹⁴⁹ G. Tarrago, A. Ramdani, J. Elguero, and M. Espada, *J. Heterocycl. Chem.* **17**, 137 (1980).

Mathias and Burkett^{149a} have also obtained two isomers in the phase-transfer alkylation of benzimidazoles (**86**), using an 18-crown-6 catalyst.



Ogilvie *et al.*¹⁵⁰ have described facile alkylation of purines and pyrimidines in THF, using tetrabutylammonium fluoride (TBAF) at room temperature. Uracil, cytosine, and adenine give mainly 1,3-dialkylation.

Tetrahydro-1,2,3,4-dioxo-2,4-quinazoline (**88**) has been dialkylated by Hedayatullah¹⁵¹ and the reaction extended to other pyrimidines.¹⁵² In all cases the corresponding N¹,N³-dialkyl derivatives are obtained in good yields. Pyrimidines are **89** (uracil): R = H, R' = H; **90** (thymine): R = Me, R' = H; **91** (5-nitrouracil): R = NO₂, R' = H; **92** (5-flourouracil): R = F, R' = H; **93** (6-chlorouracil): R = H, R' = Cl. These studies are of interest because structural deformations of nucleic acids caused by alkylating agents may be relevant to their mutagenic and carcinogenic effects on living systems.¹⁵³



^{149a} L. J. Mathias and D. Burkett, *Tetrahedron Lett.*, 4709 (1979).

¹⁵⁰ K. K. Ogilvie, S. L. Beaucage, and M. F. Gillen, *Tetrahedron Lett.*, 1663 (1978).

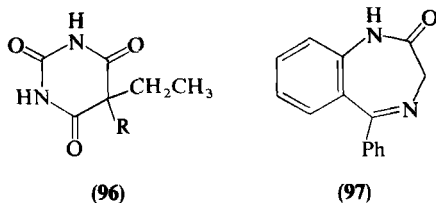
¹⁵¹ M. Hedayatullah, *C. R. Acad. Sci., Ser. C* **289**, 365 (1979).

¹⁵² M. Hedayatullah, *J. Heterocycl. Chem.* **18**, 339 (1981).

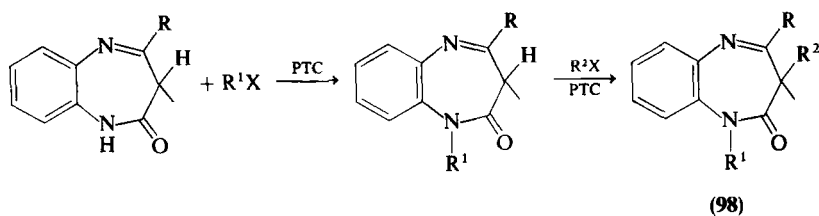
¹⁵³ T. Tanabe, K. Yamanchi, and M. Kinoshita, *Bull. Chem. Soc. Jpn.* **50**, 3021 (1977).

Vernin *et al.*¹⁵⁴ have recently described the synthesis of 1-alkyl- and 1,3-dialkyl-2-benzimidazolones from benzimidazolones, using PTC.

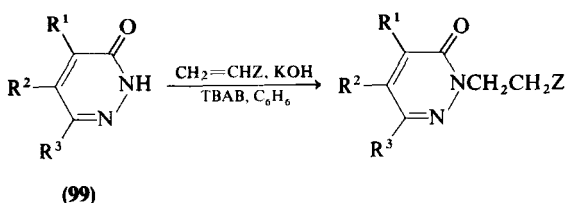
Barbiturates (96) and nitrazepan (97) have been methylated by the extractive alkylation procedure, using ICH_3 .^{155,156}



Benzodiazepine-2-ones (98) have been alkylated by Vernin *et al.*¹⁵⁷ in a two-step process, using PTC for each step. The first alkylation takes place at nitrogen.



Not only alkylations, but also Michael-type reactions, with weakly basic heterocyclic amines, can be accomplished by PTC. Yamada and Ohki¹⁵⁸ have recently reported such a reaction with pyridazinones (99).



Benzopyranobenzodiazepinones (100) have been recently prepared by Reddy and Subba¹⁵⁹, using alkylating or acylating agents in the presence of aqueous NaOH and TEBA.

¹⁵⁴ G. Vernin, H. Domloj, C. Siv, J. Metzger, and A. K. El Shafei, *J. Heterocycl. Chem.* **18**, 85 (1981).

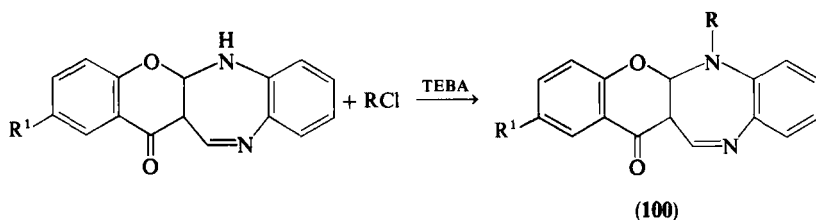
¹⁵⁵ H. Ehrsson, *Anal. Chem.* **46**, 922 (1974).

¹⁵⁶ H. Ehrsson and A. Tilly, *Anal. Lett.* **6**, 197 (1973).

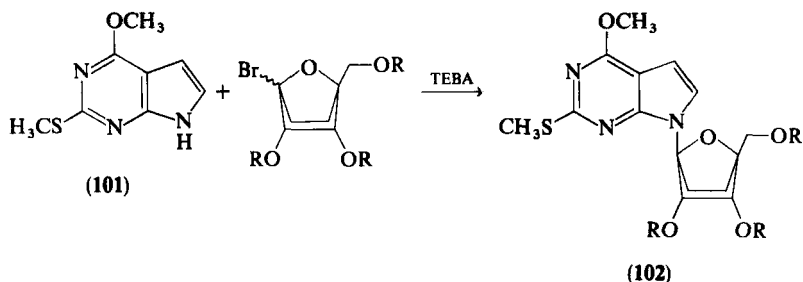
¹⁵⁷ G. Vernin, H. Domloj, C. Siv, J. Metzger, A. Archavlis, and J. R. Linas, *Chem. Scr.* **16**, 157 (1980).

¹⁵⁸ T. Yamada and M. Ohki, *Synthesis*, 631 (1981).

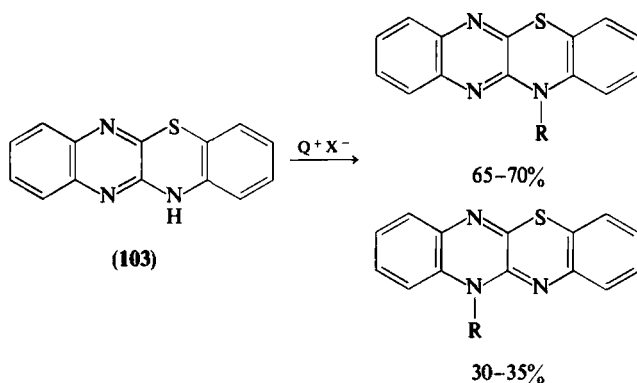
¹⁵⁹ G. J. Reddy and A. V. Subba, *Curr. Sci.* **50**, 84 (1981).



c. Heterocyclic Compounds with More than Two Nitrogen Atoms. Seela and co-workers^{160,161} have reported a phase transfer glycosidation of pyrimidine derivative **101** in the synthesis of a potential interferon inductor intermediate (**102**).



El Shafei *et al.*¹⁶² have studied the ambident reactivity of quinoxalino-[2,3*b*]-1,4-benzothiazine (**103**) and observed that under phase transfer conditions the ratio of benzothiazine N-alkylation versus quinoxaline N-alkylation was nearly 2:1.

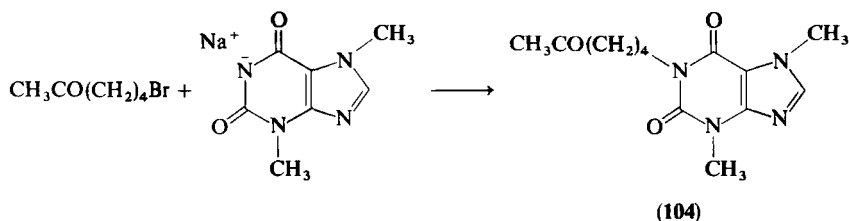


¹⁶⁰ H. D. Winkeler and F. Seela, *Chem. Ber.* **113**, 2069 (1980).

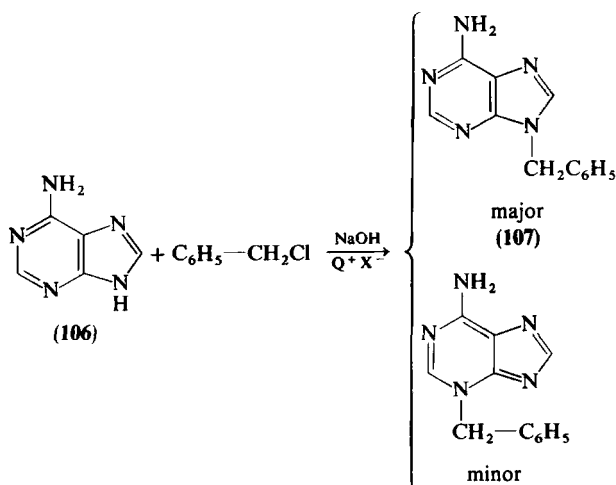
¹⁶¹ F. Seela and D. Hasselmann, *Chem. Ber.* **113**, 3389 (1980).

¹⁶² A. K. El Shafei, G. Vernin, and J. Metzger *Gazz. Chim. Ital.*, **III**, 413 (1981).

Some patents describe alkylation of theobromine derivatives under phase transfer conditions. 1-(5-Oxoheptyl)theobromine (**104**) has been prepared by alkylating the sodium salt in the presence of TBAB and toluene.¹⁶³ Theobromine (not its Na⁺ salt), and other xanthines have also been alkylated, according to Philipossian and Ensen¹⁶⁴ using NaOH and TBAHSO₄.



Adenine derivatives deserve a special comment. In most pharmaceutical applications the substituted 9-compound is the active isomer. However, during alkylation under neutral conditions position 3 is more reactive. Ogilvie *et al.*¹⁵⁰ have obtained a higher ratio of the 9-isomer, but isomer 3 was still present in significant quantities. Using the sodium or potassium salt of adenine with methyltricaprylammonium chloride, Lindblom and Elander¹⁶⁵ reported 80% of isomer 9 (**107**). Almost identical results have been described by Shinkai *et al.*¹⁶⁶ in biphasic liquid-liquid benzylation of adenine (**106**). These studies clearly indicate that PTC can give high yields and a high reaction selectivity in favor of the preferred 9-isomer.



¹⁶³ Iwashiro Seyaku Cie, Japanese Kokai 81/59,775 (1981).

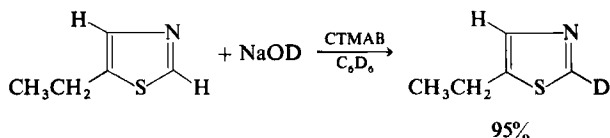
¹⁶⁴ G. Philipossian and M. Ensen, European Patent 19,165 (1980).

¹⁶⁵ L. Lindblom and M. Elander, *Pharm. Technol.* 59 (1980).

¹⁶⁶ I. Shinkai, M. C. Vanderzwan, F. W. Hartner, R. A. Reamer, R. J. Tull, and I. M. Weinstock, *J. Heterocycl. Chem.* 18, 197 (1981).

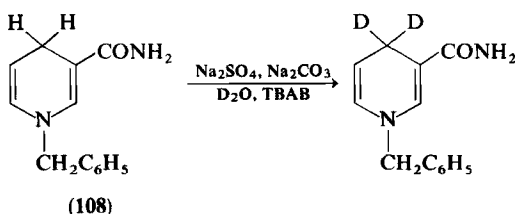
3. C-Deuterations

H/D Exchange at C-1 and C-3 positions of 2-octanone was described by Starks¹⁶⁷ in an early publication on PTC. Deuteration of heterocyclic compounds has been mainly studied by Dou and co-workers,¹⁶⁸ who showed that thiazole derivatives are deuterated conveniently and in high yield.



The use of specific salts and solvents has been studied and the rate constants of exchange have been determined.^{169,170}

Nakamura *et al.*¹⁷¹ have deuterated dihydrobenzyl nicotamide (**108**) with D₂O, in CH₂Cl₂.



B. HETEROCYCLIC NUCLEOPHILES (NUCLEOPHILIC ATOM BONDED TO THE RING)

1. C-Alkylations and C-Additions

C-Alkylations and -additions occur by prior formation of a carbanionic center bonded to the heterocycle. This carbanion will be formed only if the heterocycle contains a benzo-fused ring and/or electron-withdrawing substituents and/or a positive charge.

Hart *et al.*¹⁷² observed that pyridines cannot be alkylated on carbons bonded to positions 2, 4, or 6 unless the nitrogen atom is first quaternized.

¹⁶⁷ C. M. Starks, *J. Am. Chem. Soc.* **93**, 195 (1971).

¹⁶⁸ W. J. Spillane, H. Dou, and J. Metzger, *Tetrahedron Lett.*, 2269 (1976).

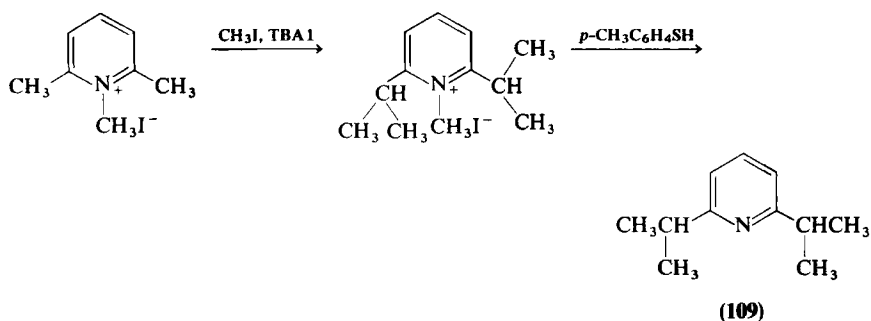
¹⁶⁹ T. Higgins, W. J. Spillane, H. Dou, and J. Metzger, *C. R. Acad. Sci., Ser. C* **284**, 929 (1977).

¹⁷⁰ W. J. Spillane, P. Kavanagh, F. Young, H. Dou, and J. Metzger, *J. C. S. Perkin II*, 1763 (1981).

¹⁷¹ K. Nakamura, A. Ohno, S. Yashi, and S. Oka, *Tetrahedron Lett.*, 4185 (1978).

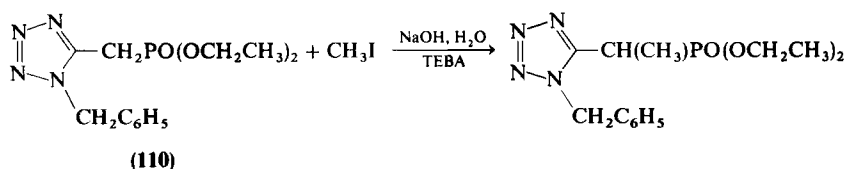
¹⁷² L. S. Hart, C. R. Killen, and K. J. Saunders, *J. C. S. Chem. Commun.*, 24 (1979).

After C-alkylation by phase transfer catalysis, the nitrogen atom is de-quaternized by 4-methylthiophenol to yield the free pyridine base **109**.

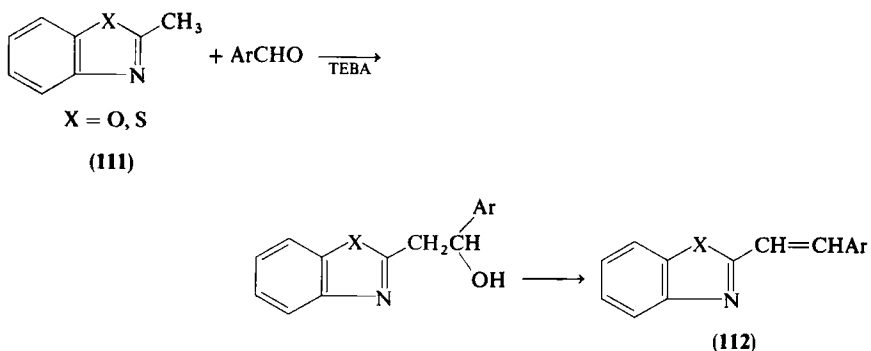


At the 4-position alkylation gives *tert*-butyl derivatives, but at 2- and 6-positions the reaction stops at the isopropyl stage for steric reasons.¹⁷³

Diethyl tetrazolomethanephosphonate (**110**) was successfully C-alkylated by Yaounnac *et al.*¹⁷⁴



Dryanska and Ivanov¹⁷⁵ have condensed 2-methylbenzoxazole and 2-methylbenzothiazole (**111**) with an aryl aldehyde to yield the corresponding substituted styrene derivative **112**. Depending on conditions, the intermediate carbinol has been isolated.

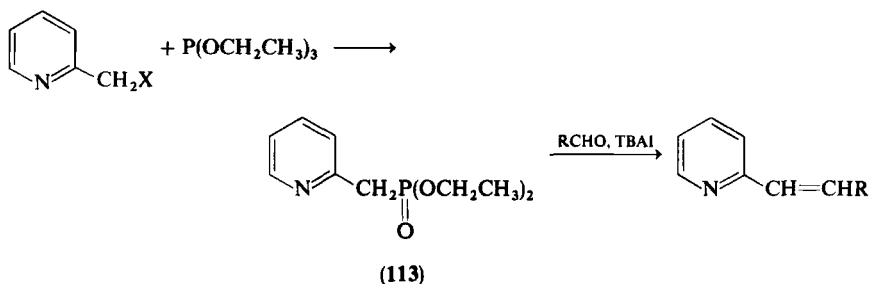


¹⁷³ U. Berg, R. Gallo, G. Klatte, and J. Metzger, *J. C. S. Perkin II*, 1350 (1980).

¹⁷⁴ J. J. Yaounnac, B. Sturz, J. L. Kraus, C. Chastel, and J. Colin, *Tetrahedron Lett.*, 2689 (1980).

¹⁷⁵ V. Dryanska and C. Ivanov, *Tetrahedron Lett.*, 3519 (1975).

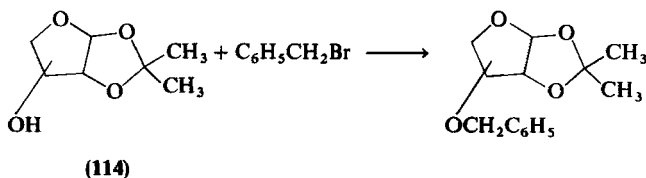
Halomethylpyridines have been used by Piechucki¹⁷⁶ in a Horner–Wittig reaction under PTC conditions.



2. O-Alkylations and O-Acylations

Two main classes of compounds have been studied: carbohydrates and hydroxyheteroaromatic compounds.

With carbohydrates a major difficulty is a high hydrophilicity of the unsubstituted protected compounds. However, strained **114** has been benzylated by Czernecki *et al.*,¹⁷⁷ using benzyl bromide with NaH and TBAI as catalyst.



Garegg *et al.*¹⁷⁸ have also carried out monobenylation of monosaccharide-diols with PhCH_2Cl in CH_2Cl_2 and $\text{TBA}^+ \text{HSO}_4^-$ catalyst.

Beaucage and Ogilvie¹⁷⁹ reported easy acylation of hydroxy groups with TBAF as catalyst; under the same conditions silyl groups are displaced.

Nouguier¹⁸⁰ has recently proposed a new method for alkylation of unsubstituted carbohydrates under phase transfer conditions (see Section V).

Hydroxyheteroaromatic molecules can be alkylated by phase transfer catalysis under conditions similar to those used for phenols.^{181,182} Alkylation

¹⁷⁶ C. Piechucki, *Synthesis*, 869 (1974).

¹⁷⁷ S. Czernecki, C. Georgoulis, and C. Provelenghion, *Tetrahedron Lett.*, 3535 (1976).

¹⁷⁸ P. J. Garegg, I. Ivensen, and S. Oscarson, *Carbohydr. Res.* **50**, 12 (1976).

¹⁷⁹ S. L. Beaucage and K. K. Ogilvie, *Tetrahedron Lett.*, 1691 (1977).

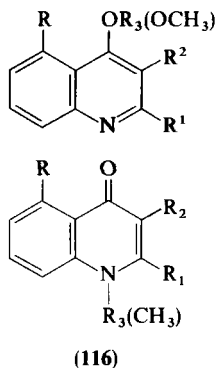
¹⁸⁰ R. Nouguier, *Tetrahedron Lett.*, 3505 (1982).

¹⁸¹ A. McKillop, J. C. Fiaud, and R. P. Hug, *Tetrahedron* **30**, 1379 (1974).

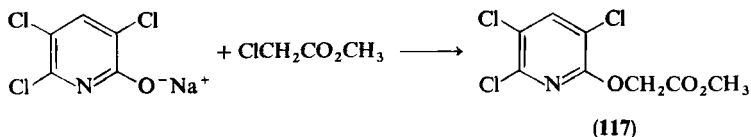
¹⁸² E. D'Incan and P. Viout, *Tetrahedron* **31**, 159 (1975).

of phenolates occurs almost exclusively at the oxygen, but anions of hydroxyaromatic molecules are usually alkylated not only at oxygen but also at nitrogen and carbon; e.g., 2-hydroxythiophenes (2-oxo-1,2-dihydrothiophenes) give several O- and C-alkylation products.¹⁸³

Renault *et al.*¹⁴⁰ have also observed O- and N-alkylation in the reaction of hydroxyquinoline anions with Me_2SO_4 or RX and TBAB as catalyst to give **116**.



2- and 4-pyridones give O- and N-alkylation (see last section), but an ester heteroanalog of the herbicide 2,4,5-T (**117**) has been prepared, according to a patent assigned to Dow Chemical,¹⁸⁴ by reaction with $\text{ClCH}_2\text{CO}_2\text{Me}$ and TEBA as catalyst.



Later Bristol *et al.*¹³⁹ have described an improved synthesis of 2-amino-3-alkoxypyridines using PTC, which yielded selectively an O-alkylated derivative without traces of any N-alkylation.

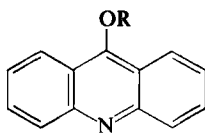
Willner and Halpern¹⁸⁵ have described quantitative O-methylation of acridone (**119**) under phase transfer conditions. But a more detailed study on alkylation of acridone under biphasic conditions by Galy *et al.*¹⁸⁶ arrives at another conclusion: the reaction gives a mixture of N- and O-alkylation products, with the N-alkyl derivative (**120**) predominating (65–100%). The yield of isolated N-alkyl derivative is 41–66%.

¹⁸³ B. Cederlund and A. Hornfeldt, *Acta Chem. Scand.* **25**, 3546 (1971).

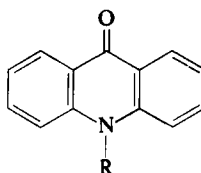
¹⁸⁴ Dow Chemical Cie, U.S. Patent 3,969,360 (1976).

¹⁸⁵ I. Willner and M. Halpern, *Synthesis*, 177 (1979).

¹⁸⁶ J. P. Galy, J. Elguero, E. J. Vincent, A. M. Galy, and J. Barbe, *Synthesis*, 944 (1979).



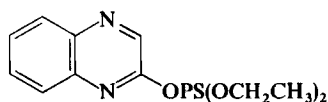
(119)



(120)

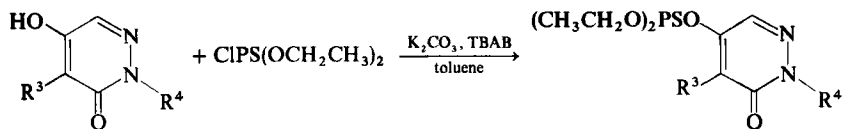
More recently Nishi *et al.*¹³¹ have reported the PTC procedure for the alkylation of acridone; alkylation takes place exclusively at the nitrogen atom.¹⁸⁶

The preparation of a quinoxalinythiophosphate (121) in biphasic systems from 2-quinoxalinone and CIPS(OEt)₂ with TBAB–NaOH has been recently described by Gore *et al.*¹⁸⁷; the reaction was catalyzed with ammonium salts and with *N*-methylimidazole.



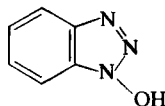
(121)

A similar type of reaction has been reported with pyridazine derivatives (122) by Konecky and Truchlik.¹⁸⁸



(122)

Feld *et al.*¹⁸⁹ have shown that 1-hydroxybenzotriazole (123), important in peptide synthesis, is O-alkylated (60–96%) under phase transfer conditions using TBACl as catalyst.



(123)

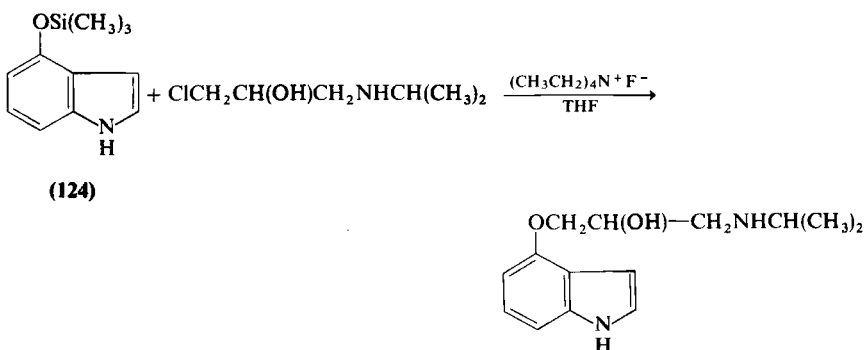
¹⁸⁷ S. T. Gore, R. N. Goel, and R. R. Sobli, Indian Patent 148,068 (1980).

¹⁸⁸ V. Konecky and S. Truchlik, Czech Patent 185,021 (1980).

¹⁸⁹ W. A. Feld, R. J. Paessun, and M. P. Serve, *J. Macromol. Sci., Chem.* A15, 891 (1981).

Galy *et al.*¹⁹⁰ studied the reaction of acridones with $\text{MeC}\equiv\text{CBr}$. Only N-alkylation was observed. However, depending on the concentration of KOH, an isomerization occurred to give the *N*-allene.

Lonza Cie¹⁹¹ has recently patented a selective O-alkylation reaction of an indole derivative starting not from hydroxy- but from trimethylsilyloxy-indole (124).

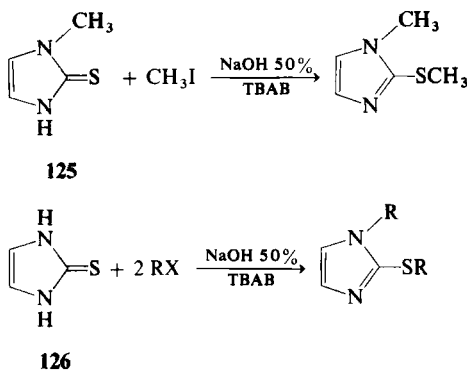


3. *S*-Alkylations

In general, alkylation of ambident S,N-nucleophilic heterocycles gives predominantly, if not exclusively, *S*-alkylated products. In some cases, however, *N*-alkylation follows *S*-alkylation to give *N,S*-dialkylated compounds.

The first example of PTC alkylation of ambident heterocyclic anions of the type $\text{N}-\text{C}-\text{S}^-$ was by Hassanaly *et al.*¹⁹²

The methylation of 1-methyl-2-thioxo-2,3-dihydroimidazole (125) with methyl iodide gives 55% yield of the *S*-alkylated product, whereas with unsubstituted 2-thioxo-2,3-dihydroimidazole (126) *N,S*-dialkylation is observed.

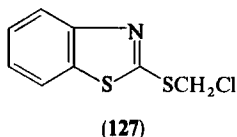


¹⁹⁰ A. Mahamoud, J. P. Galy, E. J. Vincent, and J. Barbe, *Synthesis*, 917 (1981).

¹⁹¹ Lonza Chem Cie, Japanese Kokai 81/167,668 (1981).

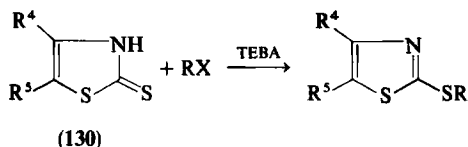
¹⁹² P. Hassanaly, H. Dou, J. Metzger, G. Assef, and J. Kister, *Synthesis*, 253 (1977).

The synthesis of chloromethylthio heterocycles, e.g., **127** had been described by Goralski and Burk¹⁹³ in the reaction of benzothiazole-2-thiones, 2-pyridinethiones, and 2-quinolinethiones with chlorobromomethane. In the case of 1,3,4-thiadiazole-2,5-dithione, the reaction was made with the pre-formed alkali metal salt.



Nasipuri *et al.*¹⁹⁴ have recently reported S-alkylation of pyrimidine derivatives.

Alkylation of 2-thiopyridone and of 2-thiobenzoxazolone has been described by Dou *et al.*¹⁹⁵ Yields are good, and only S-alkylation is detected. In a later study, Δ^4 -thiazoline-2-thione, thiazolidine-2-thione (**130**) and benzothiazoline-2-thione have been alkylated, using the phase transfer technique.¹⁹⁶



Alkylation and acylation of thioacridone are difficult because the acridine thioethers and thioesters that are formed undergo hydrolysis in alkaline medium. Vlassa *et al.*¹⁹⁷ and later Galy *et al.*¹⁹⁸ used PTC to prevent this hydrolysis, thus obtaining high yields (90–98%) of alkylation and acylation products.

4. *N*-Alkylations

To our knowledge, only one example of alkylation, under phase transfer conditions, of an amino group bonded to a heterocycle has been reported

¹⁹³ C. T. Goralski and G. A. Burk, *J. Org. Chem.* **42**, 3094 (1977).

¹⁹⁴ D. Nasipuri, S. Banerjee, B. V. Alaka, and N. P. Daw, *Synthesis*, 850 (1980).

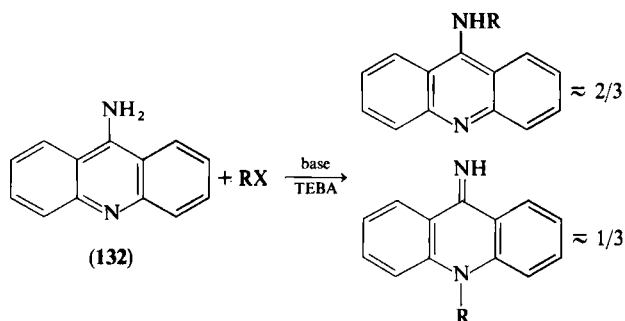
¹⁹⁵ H. Dou, P. Hassanaly, J. Kister, and J. Metzger, *Phosphorus Sulfur* **3**, 335 (1977).

¹⁹⁶ H. Dou, P. Hassanaly, G. Vernin, and J. Metzger, *Helv. Chim. Acta* **61**, 3143 (1978).

¹⁹⁷ M. Vlassa, M. Kezdi, and I. Goia, *Synthesis*, 850 (1980).

¹⁹⁸ J. P. Galy, E. J. Vincent, A. M. Galy, J. Barbe, and J. Elguero, *Bull. Soc. Chim. Belg.* **90**, 947 (1981).

and this by Galy *et al.*¹⁹⁹ The selectivity of this reaction with 9-aminoacridine (132) was discussed later.¹⁹⁸



These results are interesting because amino heterocycles show a quite different behavior under neutral and alkaline conditions, e.g., aminothiazole derivatives are alkylated at the ring nitrogen in weakly acidic and neutral media and at the exo nitrogen in highly alkaline medium.²⁰⁰ Therefore, the use of PTC to promote exo nitrogen alkylation of azaaromatic compounds may be of interest.

C. HETEROCYCLIC S_NAr

Phase transfer was used to catalyze nucleophilic aromatic substitutions by Makosza *et al.* in 1974.^{201,202} Zoltewicz²⁰³ has given a good early review of various methods and has compared other techniques that make use of polar solvents, transition metals, and monoelectron transfers.

In principle, PTC can be used for heterocyclic S_NAr as well. Moreover, because the approximate order of activating and deactivating ability of substituents is $\text{NO}_2 > \text{N}(\text{heterocycle}) > \text{SO}_2\text{Me} > \text{CF}_3 > \text{CN} > \text{H} > \text{Me} > \text{OMe}$, reactions with azaaromatic molecules must be easier than reactions with similar aromatic molecules. Therefore unsubstituted monohalogeno heterocycles were expected to undergo S_NAr reaction under PTC conditions.

¹⁹⁹ J. P. Galy, J. Elguero, E. J. Vincent, A. M. Galy, and J. Barbe, *Heterocycles* **14**, 311 (1980).

²⁰⁰ R. Barone, M. Chanon, and R. Gallo, *Chem. Heterocycl. Compd.* **34**, Part 2, 9 (1979).

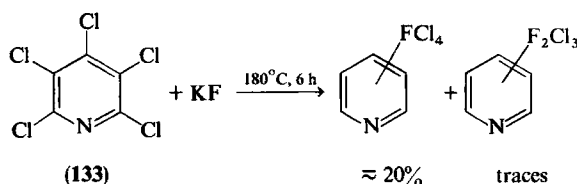
²⁰¹ M. Makosza, M. Jagustyn-Grochowska, M. Ludwikow, and M. Jawdosiuk, *Tetrahedron* **30**, 3723 (1974).

²⁰² M. Makosza and M. Ludwikow, *Angew. Chem., Int. Ed. Engl.* **13**, 665 (1974).

²⁰³ J. A. Zoltewicz, *Top. Curr. Chem.* **59**, 33 (1975).

1. Replacement by Fluoride

Halide exchange is very useful for putting fluorine into a heterocyclic ring because there are few other ways of doing this.^{204–206} The reaction with KF needs very drastic conditions when no catalyst is used, e.g., fluorination of pentachloropyridine with molten KF–KCl²⁰⁷ is carried out at 630–740°C. On the other hand, Gross and Peter²⁰⁸ showed that the complex between KF and a 2-2-2 cryptate reacts with pentachloropyridine (133) at 180°C to yield 20% of monofluorotetrachloro- and difluorotrichloropyridine.



A similar study, by Akhmetova *et al.*,²⁰⁹ indicates that reaction of pentachloropyridine with KF and 18-crown-6 in acetonitrile yields 2,4,6-trifluoro-3,5-dichloropyridine.

Finger and Kruse²¹⁰ showed that reaction of 2-chloropyridine with KF needs high temperature and very long reaction times even when dimethyl sulfone was used as solvent.

The reaction fails for 2-chloropyridine and 2-chlorothiazole under liquid–liquid biphasic conditions²¹¹ using a quaternary ammonium salt, probably because under such conditions the heterocyclic chloride is not reactive enough.

The reported examples of halogen exchange have been carried out on heterocycles activated by the presence of heteroatoms in the ring and by benzo-fusion, e.g., the preparation of 8-fluoroadenosine (137) by Kobayashi *et al.*²¹² from 8-bromoadenosine (136) and KF in acetonitrile.

²⁰⁴ A. K. Barbour, L. J. Belf, and M. W. Buxton, *Adv. Fluorine Chem.* **3**, 181 (1963).

²⁰⁵ P. Bouchet, C. Coquelet, and J. Elguero, *Bull. Soc. Chim. Fr.*, 171 (1977).

²⁰⁶ R. D. Chambers, "Fluorine in Organic Chemistry." Wiley, New York, 1973.

²⁰⁷ J. Hitzke and J. Guion, *Bull. Soc. Chim. Fr.*, 811 (1974).

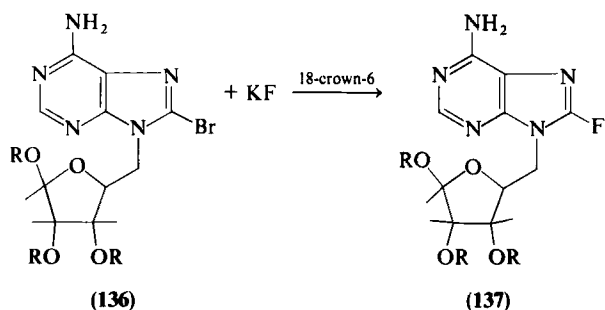
²⁰⁸ M. Gross and F. Peter, *Bull. Soc. Chim. Fr.*, 871 (1975).

²⁰⁹ N. E. Akhmetova, V. M. Vlasov, and G. C. Yakobson, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 949 (1978).

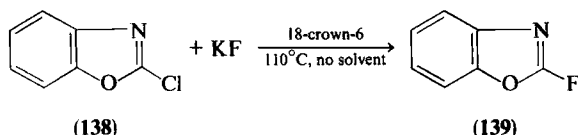
²¹⁰ G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.* **78**, 6034 (1956).

²¹¹ R. Gallo, H. Dou, and J. Elguero, unpublished results.

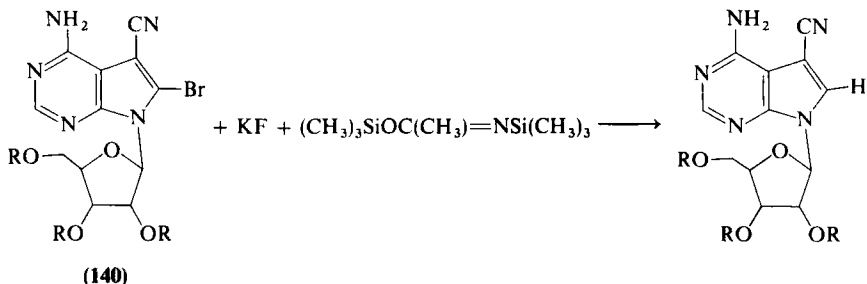
²¹² Y. Kobayashi, I. Kumadaki, A. Ohsawa, and S. I. Murakami, *J. C. S. Chem. Commun.*, 430 (1976).



Watanabe and Mukaiyama²¹³ have also converted 2-chlorobenzoxazole (138) to 2-fluorobenzoxazole (139) with KF.



In attempts to bring about halogen exchange using KF dibenzo18-crown-6 and N,O-bis(trimethylsilyl) acetamide, Townsend and co-workers²¹⁴ observed instead a reduction of 6-bromotoyocamycin (140). The reaction has been extended to 8-bromoadenosine and to 6-bromosangivamycin.



Further studies are needed to find mild reaction conditions for exchange of halogen atoms in monohalogeno heterocycles under PTC conditions.

2. Substitution by Carbanions

The first example of displacement of a chlorine atom on a heterocyclic ring by a phenylacetonitrile derivative was described by Makosza and co-workers.²¹⁵ The 9-position of the acridine ring (141) is activated because of the two benzo-fused rings.

²¹³ Y. Watanabe and T. Mukaiyama, *Chem. Lett.*, 350 (1978).

²¹⁴ F. L. Chung, R. A. Earl, and L. B. Townsend, *J. Org. Chem.* **45**, 4056 (1980).

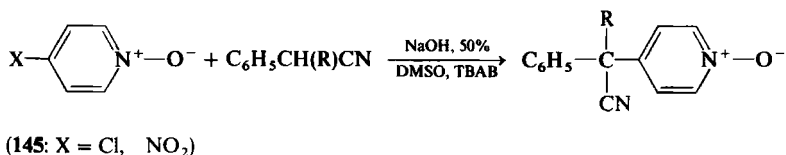
²¹⁵ W. Wilczynski, M. Jawdosiuk, and M. Makosza, *Rocz. Chem.* **51**, 1643 (1977).



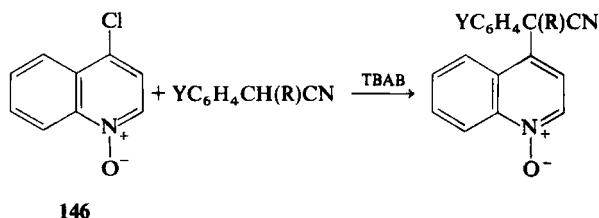
Other activated heterocycles react under these conditions, e.g., 2-chloroquinoline and 1-chloroisoquinoline.²¹⁶

If 2-chloropyridine and 2-bromopyridine could be made to react with phenylacetone nitrile derivatives under phase transfer conditions, then the method would be of interest because the compounds thus obtained are starting materials for a large series of pharmaceuticals.²¹⁷ Unfortunately, the reaction can be carried out only if an activating substituent such as a nitro group is located ortho or para to the leaving group.^{218,219}

Jawdosiuk *et al.*²²⁰ have treated 4-chloro- and 4-nitropyridine *N*-oxides (145) with substituted phenylacetone nitrile. This is in agreement with the well-known activating effect of *N*-oxides toward S_NAr reactions; the results show that nitro is a better leaving group than chloro.



Hamana *et al.*²²¹ have described similar reactions with 4-chloroquinoline 1-oxide, (146) which is more reactive than 4-chloropyridine 1-oxide because of the activating effect of the benzo-fused ring.



²¹⁶ M. Jawdosiuk, M. Ludwikow, and B. Bednarska, *Pol. J. Chem.* **53**, 85 (1979).

²¹⁷ A. Kleeman, *Chem. Zt.* **101**, 389 (1977).

²¹⁸ M. Jawdosiuk, M. Makosza, E. Malinowska, and W. Wilczynski, *Pol. J. Chem.* **52**, 2189 (1978).

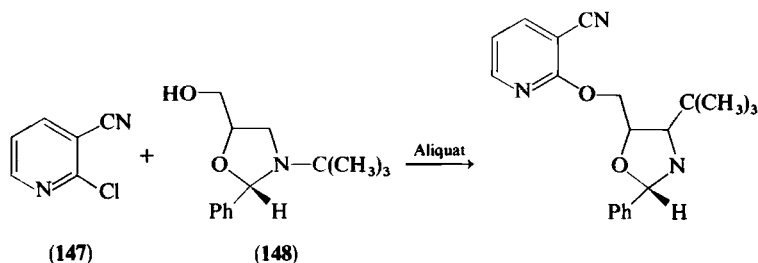
²¹⁹ H. Alsaidi, R. Gallo, and J. Metzger, *C. R. Acad. Sci., Ser. C* **289**, 203 (1979).

²²⁰ M. Jawdosiuk, M. Makosza, and W. Wilczynski, *Pol. J. Chem.* **53**, 617 (1979).

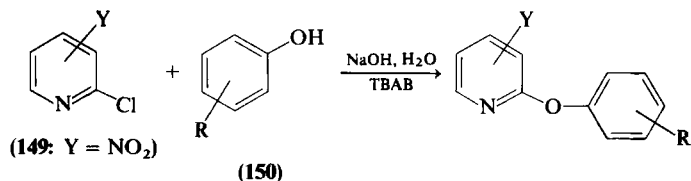
²²¹ M. Hamana, F. Sano, Y. Kimura, and H. Noda, *Heterocycles*, 371 (1978).

3. Synthesis of Heteroaryl Ethers

The synthesis of a heteroaryl alkyl ether under PT conditions is easier using alkylation of hydroxy heterocycles¹³⁸⁻¹⁴⁰ than displacement of a leaving group on heterocycles by alcoholates. The first reaction is similar to the alkylation of phenols,^{181,182,222} which gives good yields under PT conditions. The second reaction is equivalent to the S_NAr reaction, which usually occurs only with activated aromatics. However, the preparation of halogeno heterocycles is sometimes easier than the synthesis of hydroxy equivalents so that PTC heteroaryl nucleophilic substitutions using alcoholates also are of interest. According to this approach, Serioduggan *et al.*²²³ have introduced a β -adrenergic blocking moiety (**148**) on a 2-chloro-3-cyanopyridine (**147**); the reaction has been extended to other aliphatic alcohols, under liquid-liquid and solid-liquid conditions.



Heteroanalogues of biphenyl ethers have also been prepared by Alsaïdi *et al.*,²²⁴ using PTC. Several other agrichemicals have been obtained from 3-(or 5)-nitro-2-chloropyridine (**149**) and a series of substituted phenols (**150**). The yields are 70–90% and are very little dependent on the substitution in the phenol molecule. An electron-withdrawing substituent must be present in the pyridine ring because unsubstituted 2-chloropyridine does not react under these conditions. The reaction works, however, with 2-chloro- and 4-chloroquinoline, but under more severe conditions.

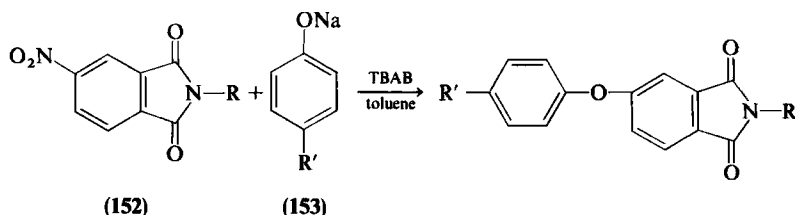


²²² D. J. Nelson and E. A. Uschak, *J. Org. Chem.* **42**, 3308 (1977).

²²³ A. J. Serioduggan, E. J. Grabowski and W. K. Russ, *Synthesis*, 573 (1980).

²²⁴ H. Alsaïdi, R. Gallo, and J. Metzger, *Synthesis*, 921 (1980).

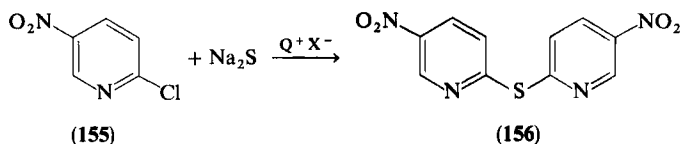
Williams²²⁵ has recently reported the synthesis of etherimides by treating halogeno- or nitroamides (**152**) with alkali metal phenoxides (**153**) in a non-polar organic solvent in the presence of a phase transfer catalyst.



4. Synthesis of Heteroaryl Thioethers

Sulfur reagents are strong nucleophiles, and heteroaryl phenyl ethers have been prepared by treating thiophenol with chloro and bromo heterocycles under PT conditions.^{196,219}

With 2-bromothiazole, however, low yields are obtained and a competitive reaction takes place because the nucleophile PhSH is alkylated by the catalyst TBAB. With 5-nitro-2-chloropyridine (**155**), bipyridyl sulfide (**156**) is prepared in high yield by disubstitution with Na₂S.²¹⁹



5. Synthesis of Heteroarylamines

4-Dialkylaminopyridines, which are active acylation catalysts, have been prepared by Patell and Sparrow,²²⁶ using secondary amines and 4-bromopyridine hydrochloride under liquid-liquid PT conditions.

Because the pK_a of dialkylamine, as determined by Bordwell,²²⁷ is so high (~ 35), these molecules cannot be converted to their anions under conditions that make use of aqueous sodium hydroxide. The catalytic effect observed is probably more complex.

Vögtle and co-workers²²⁸ have shown that the complex formed when mixing stoichiometric amounts of 18-crown-6 and of potassium phthalimide

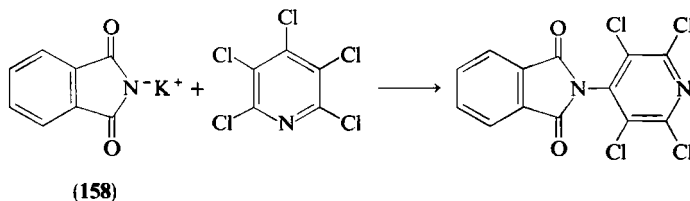
²²⁵ F. J. Williams, Ger. Offen. 3,017,670 (1980).

²²⁶ K. M. Patel and J. T. Sparrow, *Synth. Commun.* **9**, 251 (1979).

²²⁷ F. G. Bordwell, *Pure Appl. Chem.* **49**, 963 (1977).

²²⁸ W. Rasshofer, G. Oepen, and F. Vögtle, *Isr. J. Chem.* **18**, 249 (1979).

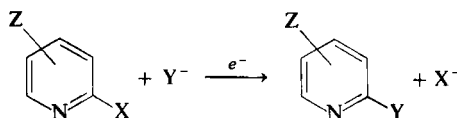
(158) reacts only at position 4 of pentachloropyridine. The same reaction with pentafluoropyridine takes place with 3 equiv of phthalimide to give 3,5-difluoro-2,4,6-tris(*N*-phthalimidopyridine) in 95% yield.



6. Synthesis of Cyano Heterocycles

The reaction of the cyanide ion with alkyl halides, using PTC, has been widely studied since the first example was reported by Starks.¹⁶⁷ However, with unactivated aryl halides (e.g., chlorobenzene and dichlorobenzene) the reaction fails.²²⁹ On the other hand, chloropyrimidine reacts with tetraethylammonium cyanide in acetonitrile.²³⁰ Hermann and Simchen²³¹ have described more generally the synthesis of cyano heterocycles, using tetraethylammonium cyanide.

The preceding examples show the possibilities and also the present limitations of PTC. The conversion of the heterocycle to its *N*-oxide or complexation of benzene with $\text{Cr}(\text{CO})_3$ promote reaction of unactivated compounds. But these approaches are based on a multistep procedure. A very promising new method is the one-step reaction of unactivated aryl (and heteroaryl) halides by way of the $\text{S}_{\text{RN}}1$ mechanism developed by Bunnett.^{232,233} This has been applied to heterocyclic molecules mainly by Wolfe and Carver.²³⁴ A pyridine derivative serves as an example.



Known leaving groups are: $\text{X} = \text{I}, \text{Br}, \text{Cl}, \text{F}, \text{SPh}, \text{NMe}_3^+, \text{and OPO}(\text{OEt})_2$ (beware of the toxicity of this group). The reaction can be carried out without an activating group. Substituents OR, OPh, or CO_2H are tolerated,

²²⁹ C. L. Liotta, F. L. Cook, and C. M. Bowers, *J. Org. Chem.* **39**, 3416 (1974).

²³⁰ H. Kobler, K. H. Schuster, and G. Simchen, *Liebigs Ann. Chem.*, 1946 (1978).

²³¹ K. Hermann and G. Simchen, *Liebigs Ann. Chem.*, 333 (1981).

²³² J. F. Bunnett, *Acc. Chem. Res.* **11**, 413 (1978).

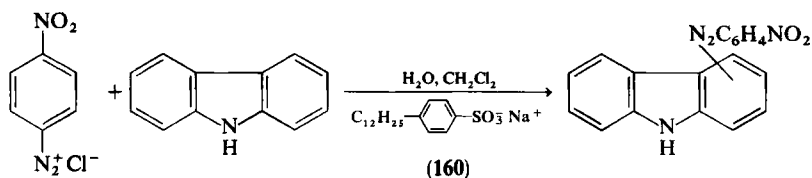
²³³ C. F. Bernasconi, *Chimia* **34**, 1 (1980).

²³⁴ J. F. Wolfe and D. R. Carver, *Org. Prep. Proced. Int.* **10**, 225 (1978).

but NMe_2 , O^- , and NO_2 interfere, and the reaction does not work as well or does not work at all. Among nucleophiles most studied have been carbanions (enolates and α -cyanoalkyl), fluorene, 1,3-pentadiene, and arene or alkane thiolates; however, alcoholates, phenolates, and stable carbanions (e.g., malonic esters) fail to react. The scope and limits of $\text{S}_{\text{RN}}1$ indicate, therefore, that the method is not equivalent or superior to PTC, but rather complementary.

D. ELECTROPHILIC HETEROAROMATIC SUBSTITUTIONS

Ellwood *et al.*^{235,236} have patented and published^{236a} information concerning diazo coupling with heterocyclic compounds whose rates were enhanced by the use of alkylaryl sulfonates (160) as PT catalysts.



This catalysis, which probably proceeds by anion exchange, gives higher reaction rates. This should be compared to the increased reactivity of diazonium ions by complexation with crown ethers, as in the examples reported by Dehmlow²³⁷ in a review on dye chemistry.

IV. Heterocyclic Ring Transformations

This section deals with transformations of heterocyclic rings and includes not only addition of carbenes and nitrenes, but also rearrangements frequently following these additions. Also included are topics such as the synthesis of Reissert compounds as well as miscellaneous oxidations and reductions.

By far, the reaction of carbenes is the most important. The 1969 paper by Makosza and Wawrzyniewicz²³⁸ described the generation of dichlorocar-

²³⁵ M. Ellwood, P. Gregory, and J. Griffiths, European Patent 28,464 (1981).

²³⁶ M. Ellwood, P. Gregory, and J. Griffiths, British Patent 79/37,296 (1981).

^{236a} M. Ellwood, J. Griffiths, and P. Gregory, *J. C. S. Chem. Commun.*, 481 (1980).

²³⁷ E. V. Dehmlow, *Chimia*, 12 (1980).

²³⁸ M. Makosza and M. Wawrzyniewicz, *Tetrahedron Lett.*, 4659 (1969).

benes using 50% aqueous sodium hydroxide, chloroform, and catalytic TEBA. The method gives comparable or superior results, compared to the conventional procedure using strong bases and anhydrous solvents,^{239,240} and it is much easier and economical.

In 1977 Julia and Ginebreda²⁴¹ reported a modification of the method by working with powdered NaOH without water; this system is preferred when unreactive olefins are used because it prevents hydrolysis of the dichlorocarbene.

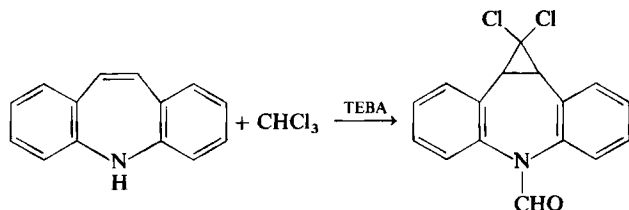
The following reactions correspond to typical additions to a double bond being part of a heterocyclic molecule.

A. ADDITION OF CARBENES TO HETEROCYCLIC MOLECULES

Several 1,1-dihalocyclopropanes have been prepared²⁴²⁻²⁴⁶ by addition of dihalocarbenes to double bonds in heterocyclic molecules.

Some dichlorocyclopropyl sugars were obtained in excellent yield by the addition of dichlorocarbene to unsaturated protected sugars in PTC systems.²⁴⁷

In the following example, the dichlorocarbene adds to the double bond and is inserted into the NH bond to give a *gem*-dichloro group, which is later hydrolyzed to an aldehyde. This reaction is related to the transformation of secondary amines to N,N-disubstituted formamides.^{248,249}



²³⁹ C. A. Bulhler, *J. Chem. Educ.* **49**, 239 (1972).

²⁴⁰ W. Kirmse, "Carbene Chemistry." Academic Press, New York, 1964.

²⁴¹ S. Julia and A. Ginebreda, *Synthesis*, 682 (1977).

²⁴² A. A. Bredikhin and V. V. Plemenkov, *Zh. Org. Khim.* **12**, 1001 (1976).

²⁴³ K. Kawashima, T. Saraio, Y. Kawano, and T. Ishiguro, *Chem. Pharm. Bull.* **26**, 942 (1978).

²⁴⁴ B. Graffe, M. C. Jaquet, and P. Maitte, *Bull. Soc. Chim. Fr.*, 350 (1979).

²⁴⁵ A. A. Bredikhin and V. P. Kostin, *Zh. Org. Khim.* **16**, 1099 (1980).

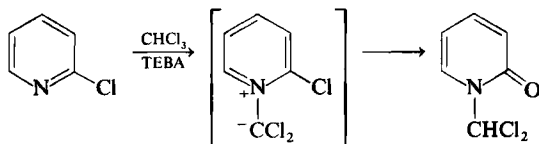
²⁴⁶ B. F. Weber and S. S. Hall, *J. Org. Chem.* **44**, 447 (1979).

²⁴⁷ P. Duchaussoy, P. Dicesare, and B. Gross, *Synthesis*, 198 (1979).

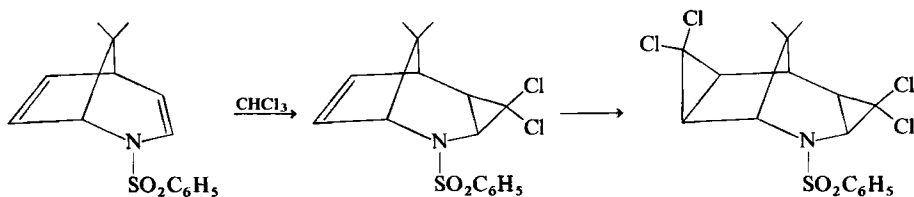
²⁴⁸ J. Graefe, I. Froehlich, and M. Muehlstaedt, *Z. Chem.* **14**, 434 (1974).

²⁴⁹ M. Makosza and A. Kacprowicz, *Rocz. Chem.*, **49**, 1627 (1975).

Arnoldi *et al.*²⁵⁰ have described a reaction in which a dichlorocarbene reacts with 2-chloropyridine by first complexing at the nitrogen atom, thereby increasing the ability of a hydroxy group to displace the chlorine in position 2.

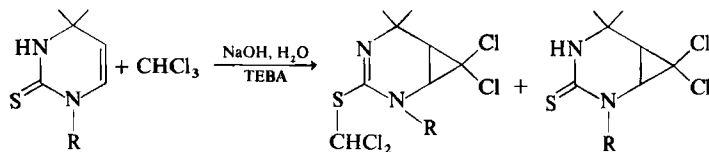


Dichlorocarbene also adds to bridged diazepine derivatives to form a bisadduct without rearrangement.²⁵¹



The addition of PTC-generated dihalocarbenes to 1-silacyclohexadiene-2,4 was reported by Märkl *et al.*²⁵²

Singh and Singh^{252a} have also described addition of dichlorocarbene to the double bond and to the sulfur atom of a thiopyrimidone derivative.



Because carbenes and nitrenes give several modifications of heterocyclic compounds,²⁵³ other reactions are likely to be reported under phase transfer conditions. Of special interest are rearrangements following addition of carbenes to heterocyclic molecules.

²⁵⁰ A. Arnoldi, R. Galli, and A. Zagni, *Heterocycles* **12**, 1335 (1979).

²⁵¹ H. Inoue, K. Tokisato, and K. Uhano, *Bull. Chem. Soc. Jpn.* **55**, 1669 (1982).

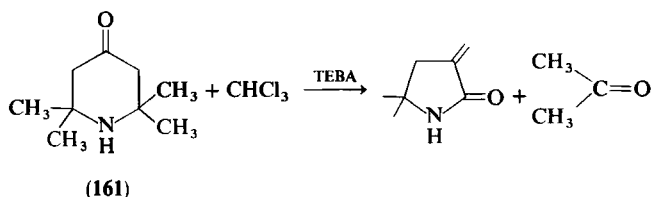
²⁵² G. Märkl, P. Hofmeister, and R. Schiessl, *Tetrahedron Lett.*, 3503 (1979).

^{252a} H. Singh and P. Singh, *Chem. Ind. (London)*, 807 (1978).

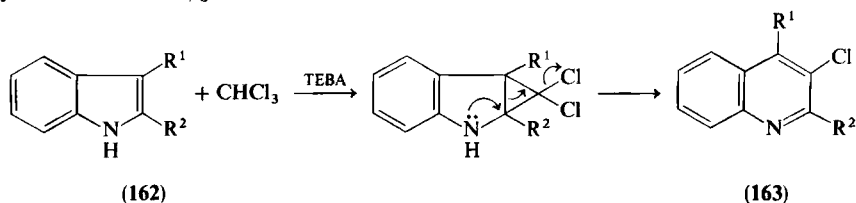
²⁵³ C. Wentrup, *Adv. Heterocycl. Chem.* **28**, 231 (1981).

B. ADDITION OF CARBENES FOLLOWED BY REARRANGEMENT

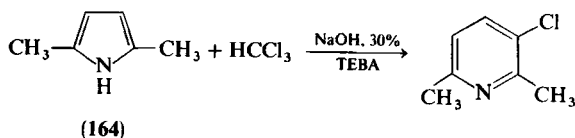
In recent attempts to formylate a 2,2,6,6-tetramethylpiperidin-4-one (**161**) with dichlorocarbene, Lind and Winkler²⁵⁴ and also Lai and Westfahl²⁵⁵ reported independently, and almost simultaneously, an unexpected formation of a pyrrolidin-2-one; the crude yield was quantitative. A reaction mechanism has been formulated.



The ring expansion of indole **162** to 3-haloquinoline **163**, induced by addition of dichlorocarbene, has been intensively studied for its mechanistic implications.²⁵⁶ A significant improvement in yield and simplicity of the reaction is reported by Kwon *et al.*,²⁵⁷ using Makosza's procedure. Dehmlow and Franke²⁵⁸ report that, depending on the substituents, the yields are 25–70%.



Deangelis *et al.*²⁵⁹ have used the method with other five-membered rings, obtaining good yields (40–70%) with substituted pyrroles **164** and imidazoles **165**.



²⁵⁴ H. Lind and T. Winkler, *Tetrahedron Lett.*, 119 (1980).

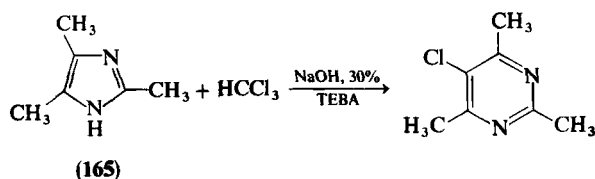
²⁵⁵ J. T. Lai and J. C. Westfahl, *J. Org. Chem.* **45**, 1512 (1980).

²⁵⁶ H. C. Van der Plas, "Ring Transformations of Heterocycles," Vol. 1. Academic Press, New York, 1973.

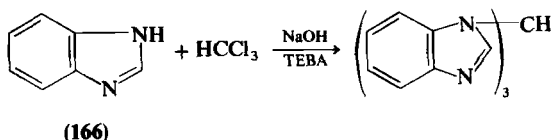
²⁵⁷ S. Kwon, Y. Nishimura, M. Ikeda, and Y. Tamura, *Synthesis*, 249 (1976).

²⁵⁸ E. V. Dehmlow and K. Franke, *Liebigs Ann. Chem.*, 1456 (1979).

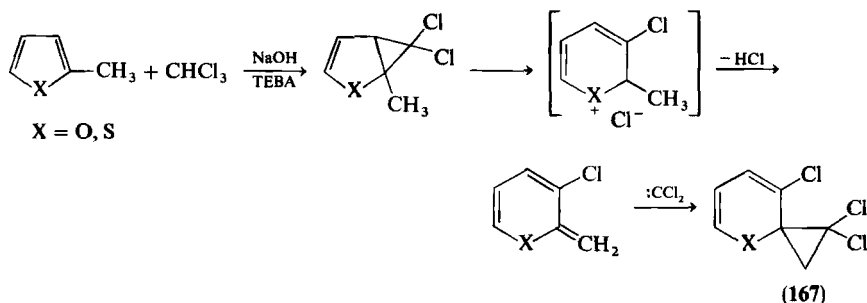
²⁵⁹ F. Deangelis, A. Gambacorta, and R. Nicoletti, *Synthesis*, 798 (1976).



With pyrazoles very few ring-expanded compounds are obtained, the main product contains three pyrazole rings attached by a nitrogen atom to a CH.²⁵⁹ A similar reaction occurs with benzimidazole²⁶⁰ (166).



Weyerstahl and Blume²⁶¹ have observed that 2-methylfuran and 2-methylthiophene with dichlorocarbene give spiro compounds 167. A mechanism has been advanced.



Other heterocyclic tertiary amines show a different behavior. Tertiary amines have been used as catalysts in dichlorocyclopropanation of olefins; they probably give an ammonium ylide as the first step in the catalytic cycle.²⁶² These ylides are usually unstable and undergo a variety of transformations such as the Stevens rearrangement and the Hoffmann elimination.

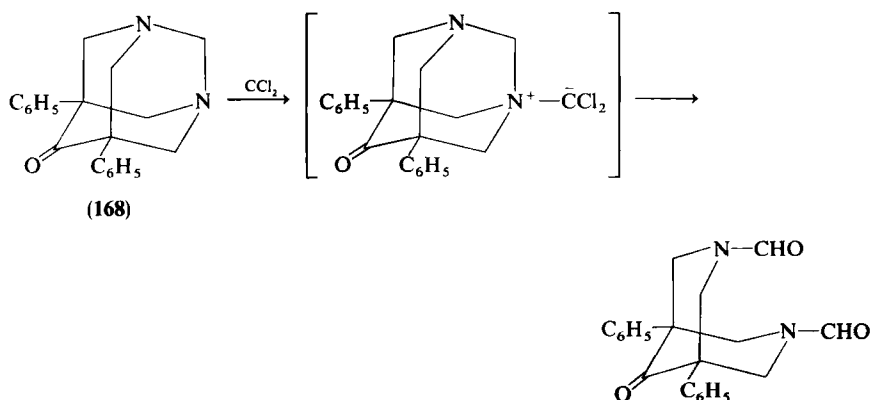
Sasaki *et al.*²⁶³ showed that tricyclic tertiary amines 168 can react with dichlorocarbene to give a bisformamide obtained from the fragmentation of the intermediate ylide.

²⁶⁰ H. Singh and P. Singh, *Chem. Ind. (London)*, 126 (1978).

²⁶¹ P. Weyerstahl and G. Blume, *Tetrahedron* **28**, 5281 (1972).

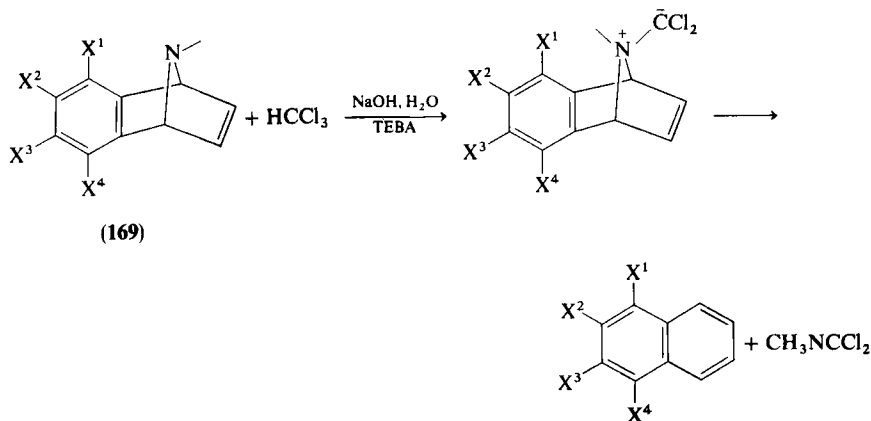
²⁶² M. Makosza, A. Kacprowicz, and M. Fedorynski, *Tetrahedron Lett.*, 2119 (1975).

²⁶³ T. Sasaki, S. Eguchi, T. Kiriya, and Y. Sakito, *J. Org. Chem.* **38**, 1648 (1973).



Casteds *et al.*²⁶⁴ described another ring-opening reaction under similar conditions.

An interesting deamination of naphthalene-1,4-imine **169** and anthracene-9,10-imine with PTC-generated dichlorocarbene was reported in 1981.²⁶⁵



C. ACYL CYANATIONS

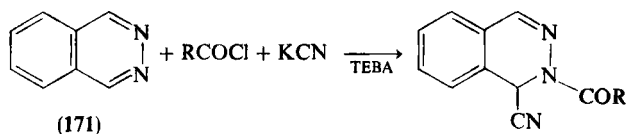
Koizumi *et al.*²⁶⁶ have reported the synthesis of Reissert compounds under PT conditions. Ulf and Budrham²⁶⁷ report the same reaction with phthalazines (171).

²⁶⁴ L. Casteds, J. Castro, and R. Riguera, *Heterocycles* **19**, 209 (1982).

²⁶⁵ G. W. Gribble, R. W. Allen, G. S. Lehoullier, J. T. Eaton, N. R. Eaton, Jr., R. I. Slayton, and M. P. Sibi, *J. Org. Chem.* **46**, 1025 (1981).

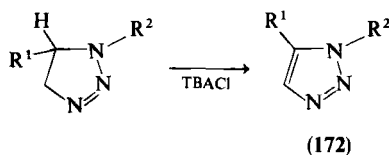
²⁶⁶ T. Koizumi, K. Takeda, K. Yoshida, and E. Yoshii, *Synthesis*, 497 (1977).

²⁶⁷ B. C. Ulf and R. S. Budrham, *Heterocycles* **6**, 1787 (1977).

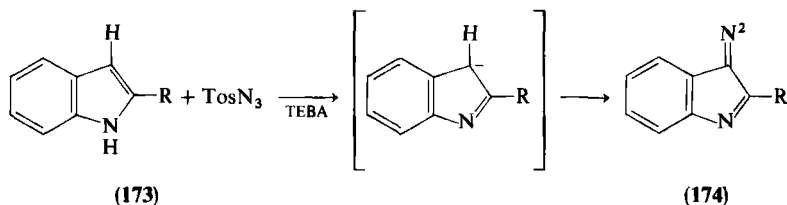


D. MISCELLANEOUS REACTIONS

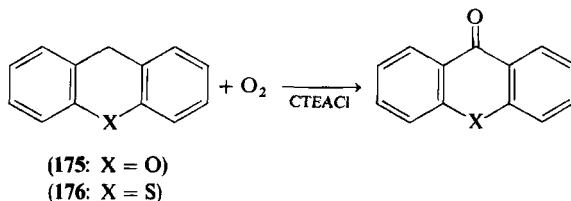
Kabada²⁶⁸ has prepared heterocyclic 5-substituted 1,2,3-triazoles (172) by oxidation of 1,2,3-triazolines with KMnO_4 under PT conditions.



Gonzalez and Galvez²⁶⁹ have described an improved method for the preparation of 3-diazoindoles (174), using PTC. Indole derivatives 173 react in position 3 because of the ambident reactivity of the molecule. Yields are 75–90% when R is acyl or heteroaryl.



Alneri *et al.*²⁷⁰ have catalyzed autoxidation of xanthone (175) and thioxanthone (176) by molecular oxygen, using PTC.



²⁶⁸ P. K. Kabada, *Synthesis*, 694 (1978).

²⁶⁹ A. Gonzalez and C. Galvez, *Synthesis*, 741 (1982).

²⁷⁰ E. Alneri, G. Bottacio, and V. Carletti, *Tetrahedron Lett.*, 2117 (1977).

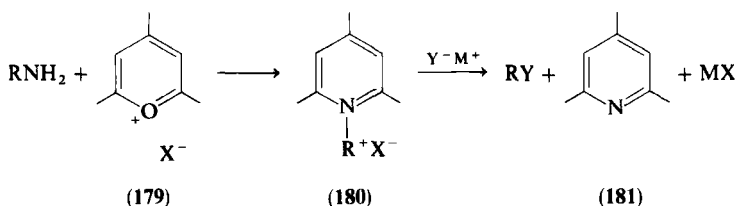
V. Heterocyclic Intermediates and Catalysts

A. THE USE OF HETEROCYCLES AS REACTION INTERMEDIATES

Heterocyclic compounds can serve as precursor, reagent, or vehicle for the preparation of nonheterocyclic compounds. This behavior of heterocycles is well described in the book by Meyers.²⁷¹

The alkylation of phthalimide has been carried out under phase-transfer conditions by Landini and Rolla,²⁷² using soluble phosphonium salts and later by Tundo,²⁷³ using heterogenous phase transfer catalysts immobilized on silica gel. Later the preparation of *N*-alkylphthalimide has been carried out directly from phthalimide by Santaniello and Ponti.²⁷⁴

In 1980 Katritzky reported the development of a new general method to convert primary amines, which are generally very poor leaving groups, to a large variety of other functional groups.²⁷⁵ This chemistry of the amino group consists of the conversion of the primary amine to the pyridinium salt **180** by addition to the appropriate pyrylium salt **179** and then displacement of the pyridine **181** by a nucleophilic reagent. This second step has been carried out in the presence of a phase transfer catalyst.²⁷⁶



Dorofeenko²⁷⁷ has shown that 2,4,6-trimethylpyrylium perchlorate did not enter reactions with active methylene compounds under PT conditions.

An interesting method has been proposed in 1982 by Nougier¹⁸⁰ in order to alkylate hydrophilic substances such as carbohydrates. Under normal PTC conditions, alkylation of these polyhydroxy compounds is difficult, and yields are low.

Nougier first developed a new method to protect selectively the sugars at the primary alcohol function, using the conventional agent dihydropyran

²⁷¹ A. I. Meyers, "Heterocycles in Organic Synthesis." Wiley, New York, 1973.

²⁷² L. Landini and F. Rolla, *Synthesis*, 389 (1976).

²⁷³ P. Tundo, *J. C. S. Chem. Commun.*, 641 (1977).

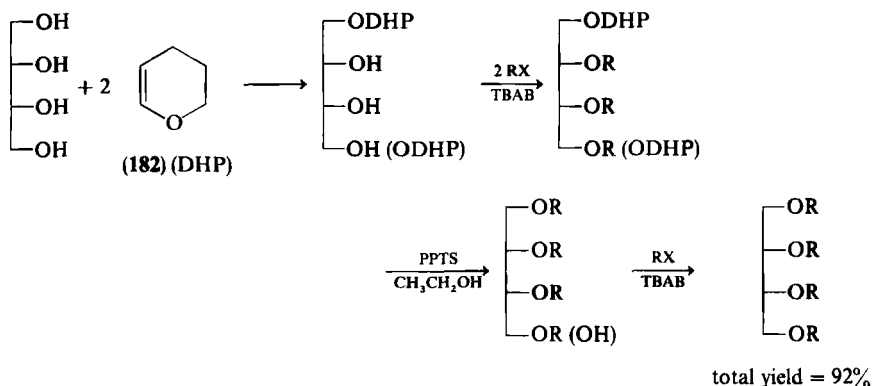
²⁷⁴ E. Santaniello and F. Ponti, *Synth. Commun.* **10**, 611 (1980).

²⁷⁵ A. R. Katritzky, *Tetrahedron* **36**, 679 (1980).

²⁷⁶ A. R. Katritzky, A. Saba, and R. C. Patel, *J. C. S. Perkin II*, 1492 (1981).

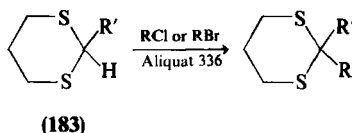
²⁷⁷ G. N. Dorofeenko, A. V. Koblik, and K. F. Suzdalev, *Zh. Org. Khim.* **17**, 1050 (1981).

DHP (182) with DMSO and HCl.²⁷⁸ The compound thus obtained was made lipophilic and was alkylated by PTC in high yield. The DHP was then removed almost quantitatively. The deprotected OH groups were etherified by using a phase transfer technique. The overall yield is 92%.¹⁸⁰



A general method for converting an aldehyde to a ketone consists of the transformation of the aldehyde to a 1,3-dithiane (183), removal of a proton by butyllithium, and alkylation, followed by hydrolysis. The method is known as the “umpolung” (reversed) carbonyl alkylation.²⁷⁹

The difficult step of alkylation with BuLi could be improved by using PTC. In fact, when R is alkyl, the acidity of the hydrogen atom in the 1,3-dithiane 183 is too high and the carbanion is not formed. On the other hand, Lissel²⁸⁰ has been able to carry out the alkylation step under PT conditions when R' is an electron-withdrawing group, e.g., CO₂Et.



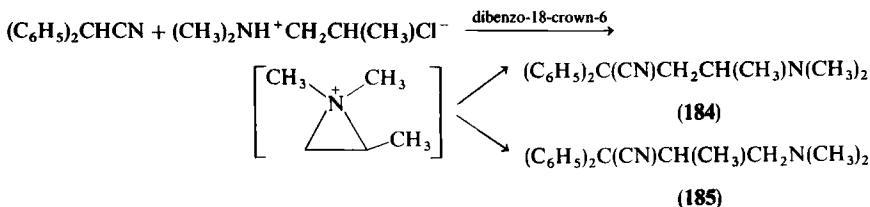
An interesting example of yield and selectivity increases in the synthesis of a methadone intermediate (184) has been described by Poupaert *et al.*²⁸¹ The yield is higher (86%) and the selectivity 184/185 increased compared to the method using toluene and NaH. In fact, the improvement is probably due to a difference in reactivity of the aziridinium ion intermediate.

²⁷⁸ R. Nougier, *Tetrahedron Lett.*, 2951 (1982).

²⁷⁹ D. Seebach, *Synthesis*, 17 (1969).

²⁸⁰ M. Lissel, *Synth. Commun.* **11**, 343 (1981).

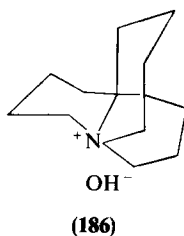
²⁸¹ J. H. Poupaert, P. Vanderjengd, B. Gerardy, M. Claesen, and P. Dumont, *J. Chem. Res., Synop.*, 192 (1981).



B. HETEROCYCLIC COMPOUNDS USED AS CATALYSTS

1. Heterocyclic Quaternary Ammonium Salts

Quaternary ammonium salts of heterocyclic compounds have been used in liquid-liquid phase-transfer syntheses. When these compounds are achiral, they show a behavior very similar to that of other quaternary ammonium salts. For example, 2-dialkylamino-1-alkylpyridinium tetrafluoroborates have been used by Tanaka and Mukayama²⁸² in the alkylation of active methylene compounds: PhCH_2CN , $\text{PhCH}(\text{Et})\text{CN}$, and $\text{PhCH}(\text{Me})\text{COPh}$. However, comparative studies of the efficiency of the catalysts show that alkylpyridinium bromides²⁸³ or *N*-alkyl-*N*-benzyl-piperidinium chloride²⁸⁴ have a smaller catalytic activity compared to tetraalkylammonium halides. McIntosh²⁸⁵ has described the preparation of azapropellane salts **186** as potential chiral phase transfer catalysts.



In this series of compounds, the chiral center is located at the nitrogen atom; whereas most chiral catalysts used for asymmetric induction have a chiral center removed from the nitrogen atom and, moreover, contain a hydroxy group β to the nitrogen atom, which may lead to the decomposition

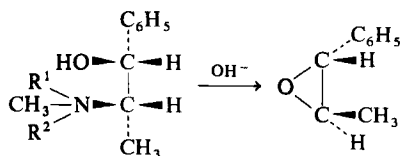
²⁸² T. Tanaka and M. Mukayama, *Chem. Lett.* **17**, 1381 (1976).

²⁸³ A. W. Herriott and D. J. Picker, *J. Am. Chem. Soc.* **97**, 2345 (1975).

²⁸⁴ M. Makosza and B. Serafinova, *Rocz. Chem.* **39**, 1223 (1965).

²⁸⁵ J. M. McIntosh, *Can. J. Chem.* **58**, 2604 (1980).

of the catalyst with subsequent formation of optically active epoxides (e.g., with ephedrinium compounds).¹



2. Heterocyclic Amines

Heterocyclic amines have also been used as phase transfer catalysts. However, because these amines quaternize easily, the question is whether the operative catalyst is the tertiary amine or the quaternary ammonium salt formed *in situ*; Furukawa *et al.*²⁸⁶ have shown that a methyl 2-pyridyl sulfoxide may be used as a phase transfer catalyst and promote substitution reactions between lithium chloride or sodium cyanide and benzyl bromide. According to the authors, the catalyst behaves as a cation complexer and not as a quaternary ammonium salt formed *in situ* by a Menshutkin reaction.

Furukawa *et al.*²⁸⁷ have compared the activity of pyridyl sulfones and sulfoxides with that of sulfides.

Reeves and Hilbrich²⁸⁸ have reported the catalysis by pyridines of benzyl ketone alkylation; they are less efficient than aliphatic trialkylamines. Reeves and White²⁸⁹ have also described the reaction of alkyl bromides with sodium cyanide, where pyrazine is a better catalyst (99% yield) compared to pyridine (12% yield). Isakawa *et al.*^{289a} have also carried out addition of dichlorocarbene to cyclohexene under biphasic conditions, using heterocyclic amines as catalysts (e.g., *N*-butylpiperidine gives 76% yield).

The reaction between potassium acetate and benzyl chloride to give the ester is catalyzed by polyamines, including heterocyclic diamines.³⁵

A study of the mechanism of catalysis of polyamines shows, however, good evidence of *in situ* formation of a quaternary ammonium salt^{36,290} having very similar catalytic activity.

²⁸⁶ N. Furukawa, K. Kishimoto, S. Ogawa, T. Kawai, H. Fujihara, and S. Oae, *Tetrahedron Lett.*, 4409 (1981).

²⁸⁷ N. Furukawa, S. Ogawa, T. Kawai, K. Kishimoto, H. Fujihara, and S. Oae, *Heterocycles* **16**, 1927 (1981).

²⁸⁸ W. P. Reeves and R. G. Hilbrich, *Tetrahedron* **32**, 2235 (1976).

²⁸⁹ W. P. Reeves and M. R. White, *Synth. Commun.* **6**, 193 (1976).

^{289a} K. Isakawa, Y. Kimura, and S. Kwon, *J. Org. Chem.* **39**, 3171 (1974).

²⁹⁰ G. W. Gokel and B. J. Garcia, *Tetrahedron Lett.*, 1743 (1978).

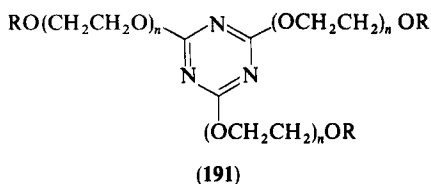
3. Crown Ethers and Cryptates

Crown ethers and cryptates represent new classes of heterocyclic catalysts having the ability to complex cations and thereby to promote solid-liquid phase transfer catalysis. A detailed description of their properties is found in the literature.^{12,21-31}

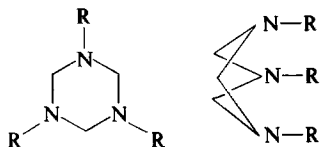
4. Chelating Catalysts

A variety of open-chain complexers, with repeating ethylenoxy or ethylenamino units $[-(\text{OCH}_2\text{CH}_2)_n]$ or $[-\text{NRCH}_2\text{CH}_2)_n]$ have been used as phase transfer catalysts. The following compounds contain heterocyclic subunits.

"Polypodes" (ethers) have been prepared by Montanari and co-workers^{37,38} from a triazine framework (191).

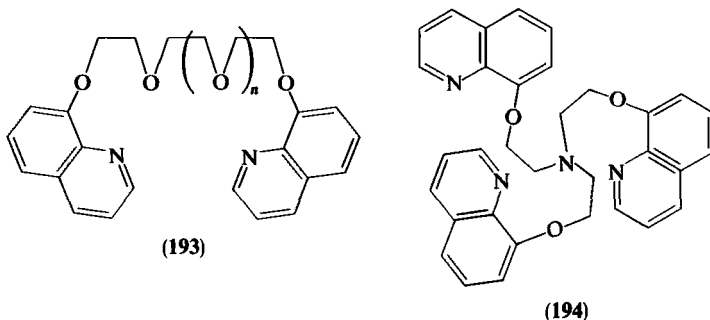


A class of macrocyclic polyethers built on a triazine ring (192) have been proposed in 1981 by Au.²⁹¹ These compounds are active as phase transfer catalysts in the conversion of $\text{C}_8\text{H}_{17}\text{Br}$ to $\text{C}_8\text{H}_{17}\text{OPh}$. These molecules have chelating arms properly arranged in order to trap cations.



²⁹¹ A. T. Au, U. S. Patent 4,266,054 (1981).

Vögtle *et al.*^{28,292,293} have also described open-chain equivalents of crown ethers (**193**) and cryptates (**194**) having heterocyclic substituents, such as quinoline.



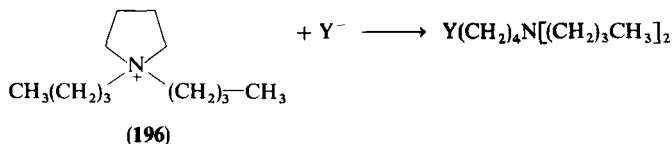
Newkome *et al.*²⁹⁴ have reviewed the preparation of synthetic macrocyclic compounds possessing heterocyclic subunits, more specifically, pyridine, furan, and thiophene.

5. Heterocyclic Quaternary Ammonium Salts, Reagents, and Catalysts

Quaternary ammonium salts are known to form ion pairs with nucleophilic anions and to transfer these reagents in organic media. Dou *et al.*¹⁴² have shown that they may also take part in a substitution reaction where the anion is the nucleophile and a tertiary amine is the leaving group.



Elguero and Espada²⁹⁵ have used this dealkylation reaction with quaternary salts of heterocyclic compounds. Another application is the preparation of tertiary amines functionalized in the δ position.²⁹⁶ In these reactions, the ammonium salt **196** is both the catalyst and the reagent.



²⁹² F. Vögtle, W. Müller, W. Wehner, and E. Buhleir, *Angew. Chem., Int. Ed. Engl.* **16**, 548 (1977).

²⁹³ F. Vögtle and H. Sieger, *Angew. Chem., Int. Ed. Engl.* **16**, 396 (1977).

²⁹⁴ G. Newkome, J. D. Sauer, J. M. Roper, and D. C. Hager, *Chem. Rev.* **77**, 513 (1977).

²⁹⁵ J. Elguero and M. Espada, *C. R. Acad. Sci., Ser. C* **287**, 439 (1978).

²⁹⁶ H. Dou, P. Hassanaly, and J. Metzger, *Nouv. J. Chim.* **2**, 445 (1978).

VI. Conclusion

From the material presented in this chapter one can conclude that the PTC methodology has already gained wide application in the chemistry of heterocyclic compounds. This is not surprising inasmuch as it offers extremely convenient conditions for a variety of heterocyclization reactions as well as for numerous modifications of heterocyclic molecules. Most of such reactions were or can be carried out under traditional conditions, but PTC usually increases the yields and purity of the products and provides a much simpler procedure for the reactions and for the isolations of the products. There are also many reactions that do not proceed satisfactorily unless conducted under PTC conditions.

The main advantages connected with the application of PTC in heterocyclic chemistry are the same as for the general application of this methodology.

1. Simplicity of the procedure. Usually the reactions are carried out by simply stirring a two-phase system (liquid-liquid or liquid-solid). The organic phase contains the organic reactants and the catalyst, usually a TAA salt. The products are easily isolated after separation of the phases.

2. Usually PTC reactions can be carried out without organic solvents or, if necessary, using solvents in small quantities sufficient to dissolve the reactants.

3. For the generation of carbanions, carbenes, etc., sodium hydroxide can be used as a base. Thus use of dangerous, expensive, and inconvenient reagents (*t*-BuOK, NaNH₂, or NaH) is eliminated. Thanks to this, the use of large quantities of meticulously dried organic solvents is also avoided.

4. In spite of the simplicity of PTC procedures, they usually assure higher yields, purity, and selectivity of the desired products formation.

5. PTC conditions are extremely convenient for industrial processes not only for the reasons shown in paragraphs 1-4 but also because of easy control, possibility for automation, and minimization of industrial wastes.

There are, of course, some limitations on the use of PTC. First of all, this approach is restricted to reactions of anions. Among reactions of anions there are some cases in which lipophilic ion pairs cannot be formed because of high hydrophilicity of the anions. On the other hand, generation of organic anions, particularly carbanions from weak acids, is somewhat restricted because of limited basicity of alkali hydroxides. Typically, CH acids of pK_a value exceeding 24 cannot be efficiently deprotonated under PTC conditions.

Thus PTC is not a universal methodology; nevertheless, it is very versatile, the scope of application is vast, and when it can be applied, it offers many advantages.

There is no doubt that PTC will be widely applied in a variety of processes similar to those described in this chapter. Its field of application in heterocyclic chemistry should expand considerably in the future.

Besides the application of this technique for synthesis and transformations of a variety of heterocyclic systems on a laboratory scale, PTC is used for manufacturing heterocyclic compounds for pharmaceutical, plant protection, or other applications.

ACKNOWLEDGMENTS

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One of us (R. J. G.) would like to thank Kansas State University for a visiting professorship during the tenure of which part of this work was prepared. The members of the Department of Chemistry of KSU are thanked for their hospitality.

Electrolysis of *N*-Heterocyclic Compounds (Part II)

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I. Introduction

In Volume 12 (1970)¹ of this series a chapter with the same title appeared (Part I); developments between 1969 and 1982 will be discussed in the following chapter. Neither the fundamental problems and experimental techniques nor the different reactions already treated in Part I will be discussed in this chapter, and it will thus be an advantage to have read Part I before beginning this chapter.

Some reviews²⁻⁴ on different aspects of the electrochemistry of heterocyclic compounds give supplementary information; besides newer material they also cover the older literature. The electrochemistry of biologically important molecules has been treated in a monograph⁵, in which many heterocyclic system are also discussed in detail.

The industrial and pilot plant applications of electrochemistry of pyridine derivatives will be included in a later chapter⁶ in this series; that chapter will give a description of electrochemical cells employed in large-scale electrochemical synthesis and the problems in scaling up laboratory processes; these problems are also treated in some books.^{7,8}

II. Methods

A. ELECTROANALYTICAL TECHNIQUES

Several types of electroanalytical techniques may be used to gain knowledge concerning the reaction mechanism of an electrolytic reaction and to determine the optimal conditions for an electrosynthesis. The use of classical polarography was illustrated in part I.¹ The different electroanalytical techniques have been treated comprehensively in a monograph,⁹ and the use of

¹ H. Lund, *Adv. Heterocyclic Chem.* **12**, 213 (1970).

² H. Lund, in "Organic Electrochemistry" (M. M. Baizer and H. Lund, eds.), Chapter 17. Dekker, New York, 1983.

³ H. Baumgärtel and K.-J. Retzlav, in "Encyclopedia of Electrochemistry of the Elements" (A. J. Bard and H. Lund, eds.), Vol. 15. Dekker, New York, 1984.

⁴ J. Armand and J. Pinson, in "Physical Methods in Heterocyclic Chemistry" (R. R. Gupta, ed.), Vol. 7, Chapter 8. Wiley, New York, 1983.

⁵ G. Dryhurst, "Electrochemistry of Biological Molecules." Academic Press, New York, 1977.

⁶ J. F. Toomey, in "Advances in Heterocyclic Chemistry" (A. R. Katritzky and A. J. Boulton, eds.). Academic Press, New York (to be published).

⁷ N. L. Weinberg and B. V. Tilak, eds., "Technique of Organic Synthesis, Scale-up and Engineering Aspects." Wiley, New York, 1982.

⁸ D. E. Danly, in "Organic Electrochemistry" (M. M. Baizer and H. Lund, eds.), Chapter 30. Dekker, New York, 1983.

⁹ A. J. Bard and L. R. Faulkner, "Electrochemical Methods." Wiley, New York, 1980.

such methods has been discussed in reviews.^{4,10} Here only one of the most used techniques, cyclic voltammetry, will be treated qualitatively and some applications illustrated by examples.

Cyclic Voltammetry

A cell for cyclic voltammetry (CV) employs three electrodes, a working microelectrode, a counter electrode, and a reference electrode; the current flows between the two former, and the potential of the working electrode is determined by measuring the potential difference between that and the reference electrode.

During a CV experiment a linearly increasing potential difference is applied between the working and counter electrodes until a certain potential difference is reached, and the difference is then decreased, usually at the same speed, the sweep rate v ; the cycle may be repeated. The current i is recorded as a function of the potential E and in the case of an ideal, reversible electrode reaction the resulting curve from a reduction–reoxidation reaction assumes a shape as shown in Fig. 1. The shape of the curve may be understood from the following qualitative description.

Below a certain potential, only a few electrons in the electrode possess sufficient energy to promote a transfer of electrons from the electrode to the substrate in the solvent phase, and the resulting current is negligible. At more negative potentials, the energy of the electrons becomes higher, the rate of the heterogeneous electron transfer increases, and the current rises. With a further decrease in the electrode potential, eventually all substrate molecules arriving at the electrode are reduced immediately, and the current is then determined by the diffusion of substrate to the electrode. As the diffusion layer becomes more and more depleted of substrate molecules by reduction, the diffusion layer becomes thicker and the concentration gradient lower. The flux of unreduced material to the electrode decreases and the current becomes gradually smaller (Fig. 1). On reversal of the potential sweep, the reduced material is reoxidized.

The curve is characterized by the peak height h , the peak potentials $E_{p(c)}$ (red) and $E_{p(a)}$ (ox) (or the half-peak potentials, which may be easier to measure exactly than the peak potential because of the somewhat flattened shape of the peak), and the peak height of the anodic peak. Further information may be obtained by semiintegration whereby a curve is obtained that resembles a polarographic curve and that contains all the information of the original data, not only peak heights and peak potentials.

¹⁰ O. Hammerich, B. Svensmark, and V. D. Parker, in "Organic Electrochemistry" (M. M. Baizer and H. Lund, eds.), Chapter 3. Dekker, New York, 1983.

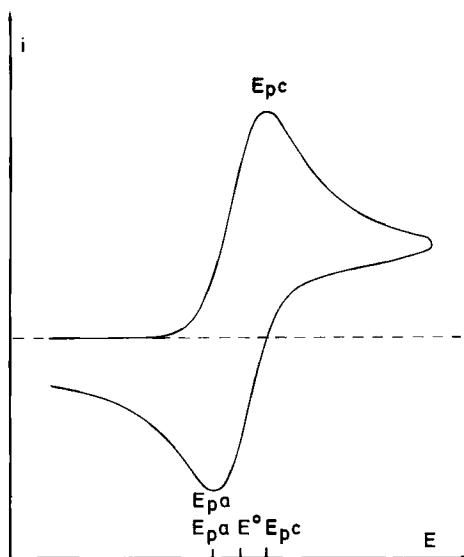


FIG. 1. Cyclic voltammogram of a reversible system, e.g., $A + e^- \rightleftharpoons A^-$. E_{pc} : cathodic peak potential; E_{pa} : anodic peak potential; E° : reversible redox potential.

The recorded current is caused not only by the heterogeneous electron transfer to the substrate (the "Faradaic current"), but also by the current used to charge the electrical double layer, which acts as a capacitor. The measured potentials include the potential drop caused by the ohmic resistance in the solution, the " iR drop." Both the charging current i_c and the iR drop grows with the sweep rate; it is always desirable to compensate for i_c and iR drop, but it becomes imperative at higher sweep rates. There exist different ways to compensate electrically for these phenomena, and this makes it possible to operate up to about 10^3 V sec^{-1} . It is assumed below that the data are obtained with proper compensation.

When the electrode reaction is a simple, reversible, fast exchange of an electron with the substrate ($A + e^- \rightleftharpoons A^-$), the peak potential E_p is independent of the concentration C and the sweep rate v . The diffusion-controlled peak height grows with the square root of v , $i_p = Kv^{1/2}$. The difference between $E_p(\text{red})$ and $E_p(\text{ox})$ is $59/n \text{ mV}$ at 25°C , where n is the number of electrons participating in the electron-transfer step.

The experimentally obtained curves do not always look like the ideal curves; this can be caused by several factors. One can be that the rate constant of the heterogeneous electron transfer, which depends on the potential, is not high compared to the time scale of the experiment. This means that it is necessary to apply a more negative potential than in the ideal case to

increase the rate of transfer of the electrons so that all of the substrate molecules are reduced on their arrival at the electrode (and a more positive potential to oxidize the reduced substrate). The peak separation $E_p(\text{ox}) - E_p(\text{red})$ is then greater than $59/n$ mV, the curves assume a "drawn-out" shape, and the reaction becomes quasi-reversible or even irreversible (Fig. 2). The heterogeneous rate constant may have a value that causes the curves to assume a reversible shape at low sweep rate but an increasingly irreversible shape at higher v . The heterogeneous rate constant may be obtained from the peak separation at a given sweep rate or from E° and the curve obtained by plotting E_p versus $\log v$.

Another complication of the reversible case may be that the reduction product A^- reacts chemically and is thus not available for reoxidation on the reverse scan, so only a small or no anodic peak is seen. In the usual electrochemical nomenclature, an electron-transfer reaction is called E and a chemical follow-up reaction C. The process in question would thus be an EC reaction; the chemical step would after a reduction in most cases be a reaction with an electrophile, including protons, a cleavage reaction, where a nucleophile is expelled, or a dimerization; for oxidation reactions with a nucleophile, loss of a proton or dimerization would be the most common follow-up reactions.

The chemical follow-up reaction causes a displacement of the peak potential for reductions to less negative potentials. At the potential where the

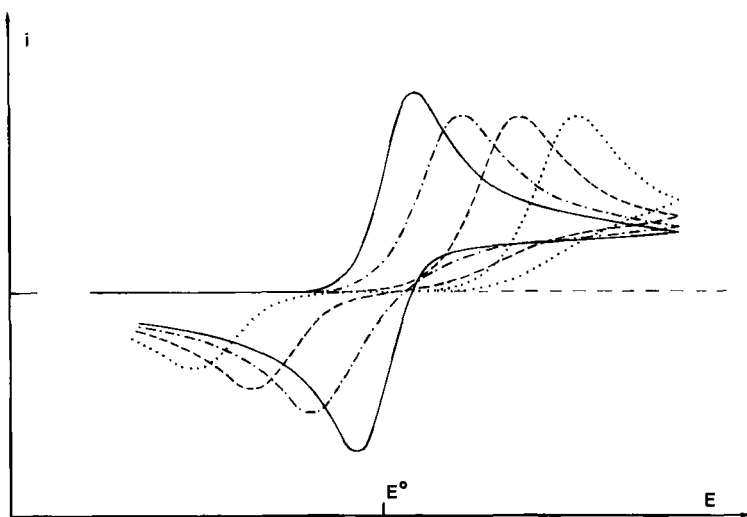


FIG. 2. Influence of value of the heterogeneous electron-transfer rate constant k_h on the shape of the cyclic voltammograms. —, $k_h = 0.1 \text{ cm sec}^{-1}$; ---, $k_h = 0.01 \text{ cm sec}^{-1}$; - - - - , $k_h = 10^{-3} \text{ cm sec}^{-1}$; ·····, $k_h = 10^{-4} \text{ cm sec}^{-1}$.

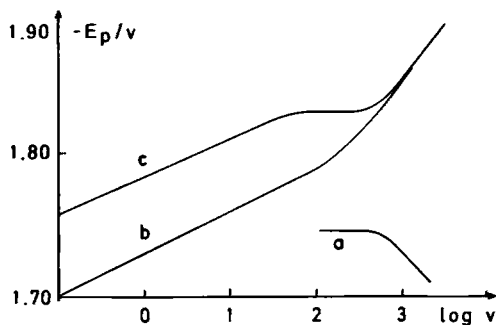


FIG. 3. Peak potentials V versus SCE of 5-chloro-8-methoxyquinoline in dependence of the sweep rate v without and in the presence of CO_2 . Curve c, cathodic peak potential without CO_2 ; a, anodic peak potential without CO_2 ; b, cathodic peak potential in the presence of CO_2 . (Reprinted from Ref. 16 with permission from *Acta Chemica Scandinavica*.)

current begins to flow, the equilibrium required by the Nernst equation is disturbed by the chemical reaction. The Nernst equation requires a certain proportion between the oxidized and reduced forms at a given potential, but if the reduced form A^- is removed from the equilibrium, then the electrode tries to reestablish the required proportion A/A^- by reducing more A , which means that the current at a given potential becomes higher than in the simple, reversible case. In a reductive EC reaction, the peak potential is thus shifted toward positive values (and toward negative values for oxidations); for a reaction with first-order kinetics, the $E_p(\text{red})$ shifts 30 mV in the positive direction when k_c is increased tenfold.

The influence of the chemical follow-up reaction depends on the ratio of the rate constant k_c of the C step and the sweep rate v . The higher that v is, the less influence does the follow-up reaction have; for chemical reactions with first-order rate constants $k_c \lesssim 10^4$, it is possible to "outrun" the reaction and obtain a reversible cyclic voltammogram at high v . The $E_p(\text{red})$ for a given system with first-order (or pseudo first-order) kinetics is then shifted 30 mV in the negative direction when v is increased tenfold.^{11–15} By plotting E_p versus $\log v$, one can get curves from which the value of k_c can be obtained. This is illustrated in Fig. 3 for a reaction where the chemical step is a cleavage.

In Fig. 3 is shown a plot of $\log v$ versus E for 5-chloro-8-methoxyquinoline (QCl), alone and in the presence of carbon dioxide.¹⁶ At slow sweep rates

¹¹ R. S. Nicholson and I. Shain, *Anal. Chem.* **36**, 706 (1964).

¹² R. S. Nicholson, *Anal. Chem.* **37**, 1351 (1965).

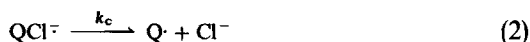
¹³ R. S. Nicholson, *Anal. Chem.* **38**, 1406 (1966).

¹⁴ L. Nadjo and J.-M. Savéant, *J. Electroanal. Chem.* **48**, 113 (1973).

¹⁵ E. Lamy, L. Nadjo, and J.-M. Savéant, *J. Electroanal. Chem.* **42**, 189 (1973).

¹⁶ P. Fuchs, U. Hess, H. H. Holst, and H. Lund, *Acta Chem. Scand., Ser. B* **B35**, 185 (1981).

only the cathodic peak is seen; the lifetime of the anion radical is too short to influence the reverse scan. The follow-up reaction is a cleavage of the primarily formed anion-radical according to Eqs. (1) and (2).



The purpose of the experiments, whose results are shown in Fig. 3, was to investigate whether the cleavage of the anion-radical was faster than the reaction of QCl^- with carbon dioxide or vice versa. If the cleavage turned out to be slower than the carboxylation, it should be possible to carboxylate QCl without loss of the Cl substituent.

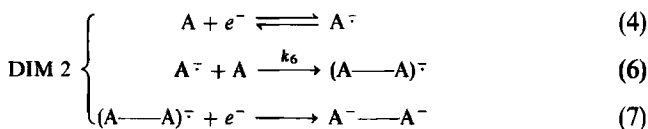
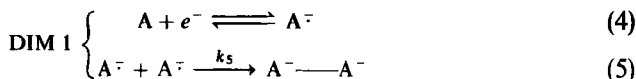
Curve c is the $E_p(\text{red})$ of QCl versus v ; at $v < \sim 10^2 \text{ sec}^{-1}$, $dE_p/d \log v$ is about -30 mV ; at $v \sim 10^2 \text{ sec}^{-1}$, the chemical reaction is being outrun, the anodic peak appears (curve a) and the voltammogram assumes the shape of a simple, reversible reaction (1) without a complicating follow-up reaction (2). From the sweep rate, where the line $dE_p/d \log v = -30 \text{ mV}$ intersects the horizontal line k_c , the first-order rate constant can be obtained.^{14,15} At still higher v the peak separation increases, which means that the heterogeneous rate constant k_h is becoming small compared to v and the voltammogram assumes the shape of a quasi-reversible system.

Curve b shows $E_p(\text{red})$ of QCl versus v in the presence of carbon dioxide. It is seen that E_p is shifted toward positive values compared to curve c and that it is not possible to outrun the chemical follow-up reaction [Eq. (3)] within the available range of sweep rates ($v \leq 10^3 \text{ V sec}^{-1}$).



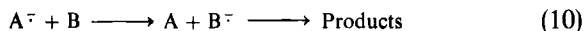
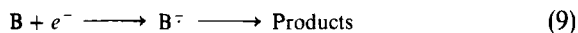
The CV investigation thus indicates that it should be possible to carboxylate 5-chloro-8-methoxyquinoline without excessive loss of chlorine. A preparative reduction at low temperature showed that it, indeed, was possible.¹⁶

If the follow-up reaction is a dimerization, this may occur in different ways; two common reaction sequences are called DIM 1 [Eqs. (4) + (5)] and DIM 2 [Eqs. (4) + (6) + (7)].^{14,15}



Inasmuch as the dimerization is a second-order reaction, the rate of the disappearance of A^\cdot depends on the concentration of A . For the uncomplicated DIM 1, one gets $dE_p/d \log v = -19.7 \text{ mV}$ and $dE_p/d \log C = 19.7 \text{ mV}$, and for DIM 2 $dE_p/d \log v = -29.6 \text{ mV}$ and $dE_p/d \log C = 29.6 \text{ mV}$.^{14,15} It is thus possible from these diagnostic criteria to distinguish between these two reaction paths, if the reaction is not complicated by a relatively slow heterogeneous rate constant (and the measured potentials are sufficiently reliable).

Quite often the electrode process would be an ECE(C) reaction, in which the second electron transfer could be a heterogeneous electron transfer from the electrode to the substrate, in which case the reaction scheme is the "classical" ECE mechanism [Eqs. (4), (8), and (9)], or the electron transfer could be a homogeneous reaction with A^\cdot as electron donor, the so-called DISP mechanism [Eqs. (4), (8), and (10)].



If the reaction of Eq. (8) is very fast, the ECE scheme would generally operate because B is formed so close to the electrode that an electron transfer from the electrode to B is feasible; if the reaction of Eq. (8) is relatively slow, B is formed far from the electrode and B will be reduced by A^\cdot , whereby A is regenerated, thus following the DISP-1 model.

The ECE mechanism may be distinguished from the simple EC scheme by the dependence of the peak height on v ; CV is, however, not well suited to distinguish ECE from DISP-1; here another technique, e.g., double-step potentiometry, may be used.

Cyclic voltammetry is also useful for the elucidation of electrocatalytic reactions; this is discussed in Section B, indirect electrochemical reactions.

Several other electroanalytical techniques may be used to illuminate a reaction sequence; these will not be mentioned here, and the reader is referred to cited literature relevant to the subject. The purpose of this section has been only to illustrate how one of the techniques can be useful in connection with preparative reactions in order to select optimal conditions. With regard to the elucidation of reaction mechanism using electroanalytical techniques, it must be remembered that these can be used to exclude the models that

do not fit the diagnostic criteria, but the mere fit of the experimental data with those of the model does not prove the model.

B. INDIRECT ELECTROCHEMICAL REACTIONS

In a direct electrolysis, the electron is exchanged between the electrode and the substrate, and the rate of the reaction depends on the electrode potential and the rate constant of the heterogeneous electron-transfer reaction. In an indirect electrolysis, the electron is primarily exchanged with a substance (a mediator) that exchanges the electron with the substrate in a "chemical" reaction, and the rate does not depend on the ability of the substrate to exchange an electron with the electrode.

Some reactions are difficult to classify; an example is reduction by means of solvated electrons, a synthetically useful method. In such a reaction the electron is ejected from the electrode into the solvent, where it has a finite lifetime before it reacts with the substrate. Reductions with solvated electrons will not be discussed here. Another example, coupling reactions, will be discussed later.

Indirect electrolysis has some advantages.

1. The direct electrolysis of a number of organic substrates requires a considerable overvoltage in order to proceed at a reasonable rate. The rate of an electron transfer in solution is high when the standard potentials of the reacting systems have suitable values.

The overvoltage may thus be diminished by using as mediator a redox couple that has a high heterogeneous rate constant.

2. Large molecules (e.g., biological macromolecules) diffuse slowly, so that the rate of direct electrolysis is low; the electroactive center may be localized in the molecule in such a way that electron transfer from an electrode is difficult, and some biologically active molecules lose their activity on contact with an electrode. These difficulties may be overcome by using a mediator.

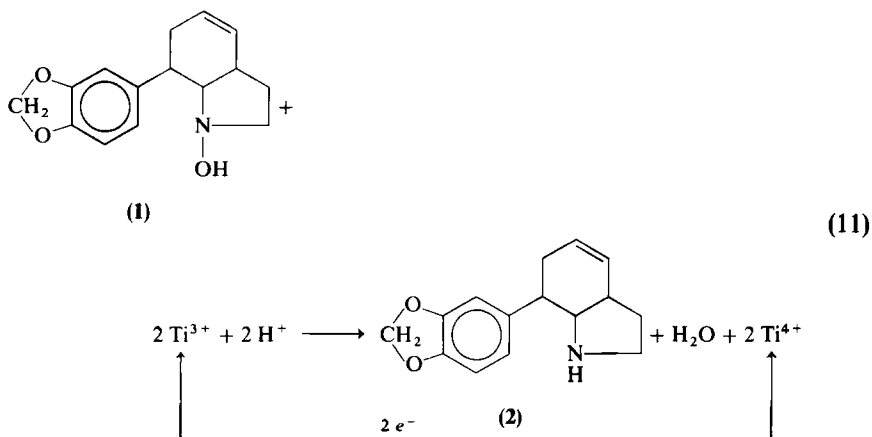
3. In some useful reactions the reagent is too expensive for large-scale preparations. In such cases regeneration of the reagent by electrolysis may be the answer.

4. In a number of synthetically interesting cases, the mediator not only exchanges an electron with the substrate but also couples with it; compounds that are difficult to obtain in other ways may be prepared by such a method.

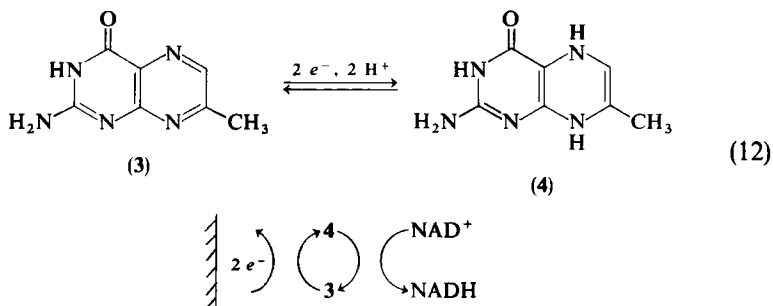
Some examples of indirect reduction by means of inorganic and organic mediators in different types of reactions will be discussed briefly; indirect oxidations may also be performed.

Titanous ions are known to reduce nitro groups to amines and also other kinds of N—O bonds to N—H. Reduction of the cyclic hydroxylamine de-

rivative **1** gave a higher yield of **2** by reduction with electrochemically regenerated titanous ions than by the conventional chemical reaction¹⁷ [Eq. (11)].



An example of the use of an organic mediator is the indirect reduction of a number of biologically important molecules such as NAD^+ , cytochrome C, hemoglobin, and insulin by the electrochemically generated 2-amino-5,8-dihydropteridone-4 **3**. The biological activity of the NADH was retained and the dimerization reaction that occurs during the reduction of NAD^+ at the electrode seemed to be absent¹⁸ [Eq. (12)].



Similarly, NADH may be oxidized to NAD^+ by a quinonoid 2-amino-dihydropteridone-4,¹⁸ prepared by anodic oxidation of the corresponding 5,6,7,8-tetrahydro derivative.

A special way to use a mediator in redox reactions is to bind it chemically to the electrode; such chemically modified electrodes may have many future

¹⁷ G. Feroci and H. Lund, *Acta Chem. Scand., Ser. B* **B30**, 651 (1976).

¹⁸ S. Kwee and H. Lund, *Bioelectrochem. Bioenerg.* **1**, 87 (1974); **2**, 231 (1975).

applications; much research is presently being devoted to this field, but it will not be discussed. The reader is referred to reviews.¹⁹⁻²¹ In a way, one could regard the use of a mediator as working with a three-dimensional modified electrode.

1. Cleavages

A number of anion-radicals and dianions of, e.g., aromatic hydrocarbons, heterocycles, and carbonyl and nitro compounds have been used as mediators in cleavages²²⁻²⁷; such mediators must be used in aprotic media such as DMF.

The reaction sequence may be formulated²²



The rate of the reaction depends on the equilibrium shown in Eq. (13), which is a function of the standard potential of A and BX, and the rate of the cleavage reaction of Eq. (14); electroanalytical techniques have been used to determine these parameters.²⁸⁻³⁰

In Eqns. (13) and (15), A is regenerated and reduced again; the electrode behaves as if the concentration of A at the electrode were higher than the bulk concentration, and the current increases. This is illustrated in Fig. 4,²⁵ where the lower curve (a) is the cyclic voltammogram of anthracene, whereas the curves b, c, and d are curves of anthracene in the presence of increasing concentrations of benzyl chloride (BX).

¹⁹ R. W. Murray, *Acc. Chem. Res.* **13**, 135 (1981).

²⁰ K. D. Snell and A. G. Keenan, *Chem. Soc. Rev.* **8**, 259 (1979).

²¹ W. R. Heineman and P. T. Kissinger, *Anal. Chem.* **50**, 166R (1978).

²² H. Lund, M. A. Michel, and J. Simonet, *Acta Chem. Scand., Ser. B* **B28**, 900 (1974).

²³ H. Lund, M. A. Michel, and J. Simonet, *Acta Chem. Scand., Ser. B* **B29**, 217 (1975).

²⁴ J. Simonet, M. A. Michel, and H. Lund, *Acta Chem. Scand., Ser. B* **B29**, 489 (1975).

²⁵ H. Lund and J. Simonet, *J. Electroanal. Chem.* **65**, 205 (1975).

²⁶ J. Sease and C. Reed, *Tetrahedron Lett.*, 393 (1975).

²⁷ V. S. Mairanovsky, *Angew. Chem.* **88**, 283 (1976).

²⁸ C. P. Andrieux, J. M. Dumas-Bouchiat, and J. M. Savéant, *J. Electroanal. Chem.* **87**, 39, 55 (1978).

²⁹ C. P. Andrieux, J. M. Dumas-Bouchiat, and J. M. Savéant, *J. Electroanal. Chem.* **88**, 43 (1978).

³⁰ J. M. Savéant and Su Khac Binh, *J. Electroanal. Chem.* **91**, 35 (1978).

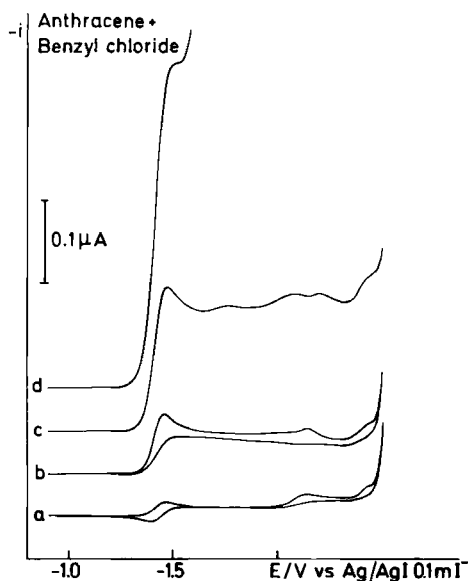
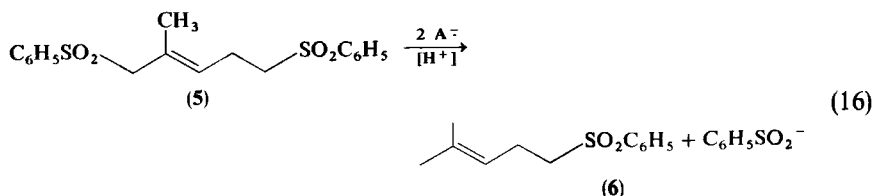


FIG. 4. Cyclic voltammograms in DMF of anthracene in the absence (curve a) and presence (b, c, and d) of increasing concentrations of benzyl chloride. (Reprinted from Ref. 25 with permission from Elsevier Sequoia S.A.)

The reaction can be used preparatively, and A, B, and X can be varied within wide limits. If a substrate has two groups eliminated at slightly different potentials, it may be possible to find an A compound with a suitable redox potential so that the rate of one of the cleavages is sufficiently faster than the other to permit a selective cleavage. The reduction of **5** to **6**, using anthracene anion-radical,³¹ illustrates the method [Eq. (16)].



It is sometimes possible to cleave substrates by this indirect method although the peak potential of the substrate is more negative than that of

³¹ J. Simonet and H. Lund, *Acta Chem. Scand., Ser. B* **B31**, 909 (1977).

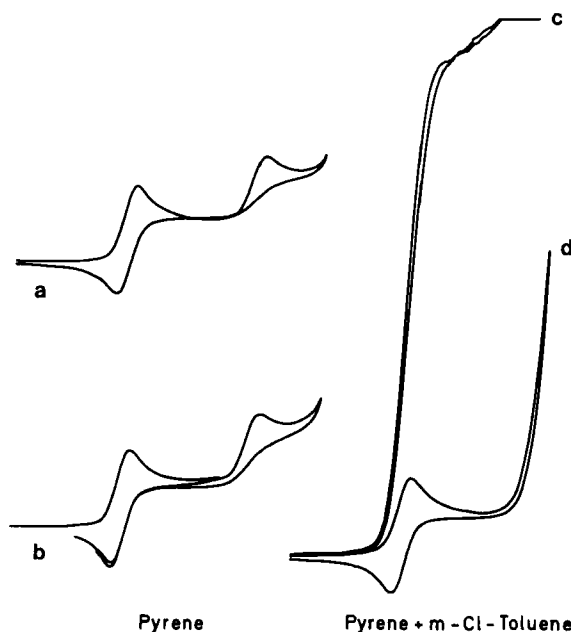


FIG. 5. Cyclic voltammograms in DMF of pyrene (a and b) and pyrene in the presence of *m*-chlorotoluene (c and d). Traces b and d are recorded without illumination, a and c with illumination of the solution ($\lambda = 500$ nm). (Reprinted from Ref. 32 with permission from *Acta Chemica Scandinavica*.)

the supporting electrolyte; isopropyl benzyl ether is thus not reducible by direct electrolysis, but by using 1-methylnaphthalene anion–radical as mediator, it is possible to cleave the compound.²³

If the reduction potential of the BX compound is too negative compared to the A compound, the ability of A^- to transfer an electron to BX may be enhanced by exciting A^- photochemically. Thus pyrene anion radical reacts very slowly with *m*-chlorotoluene, but shining green light on the red anion–radical makes the reaction proceed very fast (Fig. 5).^{32,33} Another possibility is to use the dianion; thus perylene anion–radical does not react with 1,4-dichlorobenzene, whereas it is rapidly reduced by perylene dianion.²⁵ (Fig. 6).

Oxidative cleavage by means of electrochemically generated cation–radicals is also possible; thus benzyl ethers may be cleaved and carboxylates decarboxylated using cation–radicals of brominated triphenylamines in acetonitrile containing a weak base.^{34,35} Such as indirect reaction makes it

³² H. Lund and H. S. Carlsson, *Acta Chem. Scand., Ser. B* **B32**, 505 (1978).

³³ H. S. Carlsson and H. Lund, *Acta Chem. Scand., Ser. B* **B34**, 409 (1980).

³⁴ W. Schmidt and E. Steckhan, *J. Electroanal. Chem.* **89**, 215 (1978).

³⁵ W. Schmidt and E. Steckhan, *Angew. Chem.* **90**, 717 (1978); **91**, 850 (1979).

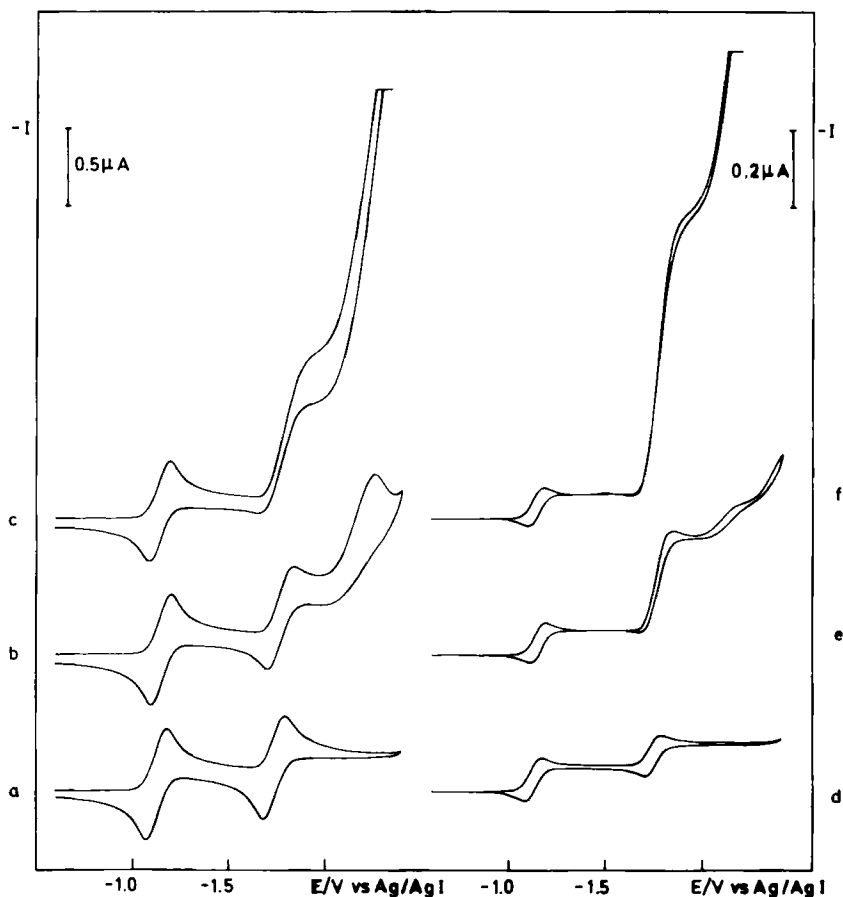


FIG. 6. Cyclic voltammograms of perylene in DMF in the absence (a and d) and presence (b, c, e, and f) of increasing concentrations of 1,4-dichlorobenzene, a, b, and c, $v = 400 \text{ mV sec}^{-1}$; d, e, and f, $v = 10 \text{ mV sec}^{-1}$. (Reprinted from Ref. 25 with permission from Elsevier Sequoia S.A.)

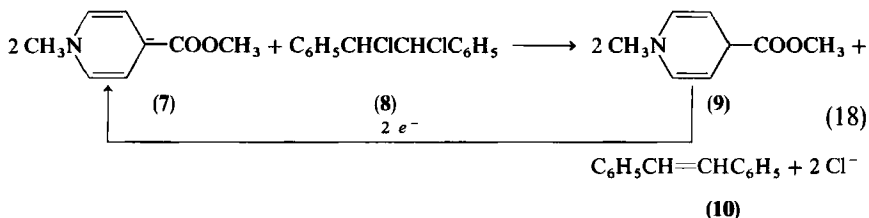
possible to perform an oxidative cleavage at a potential much lower than the irreversible oxidation potential of the substrate [Eq. (17)].



2. Eliminations

Reductive eliminations have been employed as models for electron-transfer reactions. The stereochemical differences between direct and indirect

reduction have been investigated,³⁶ and the ability of an electrochemically generated carbanion (7) to transfer an electron to a substrate (8) has been proved³⁷ using the following reaction [Eq. (18)].



Some "direct" elimination reactions may end up as "indirect" reductions; thus if RCHXCHXR (8) is reduced to $\text{RCH}=\text{CHR}$ (10), and 10 is more easily reducible than 8, then 10^- will be formed and may then be the electron-transferring species.³⁸

3. Coupling and Substitution Reactions

In a number of synthetically interesting cases, the electron transfer is followed by a coupling between the mediator and the substrate.²⁵ In the reaction sequence Eqs. (4), (13)–(15) the following reactions compete with that of Eq. (15):



or



In the reactions of Eqs. (19) and (20), the mediator A/A^- is removed from the catalytic circle by coupling with B. On the CV curves (Fig. 7) the effect is that although the peak height of the mediator A grows on addition of BX in small concentrations in a similar way, as shown in Fig. 4, the increase in peak height diminishes at higher concentrations of BX and eventually the peak height becomes independent of further increase of $[\text{BX}]$. Under such conditions, all of the A compound reacts by coupling with B.

Coupled products may also be obtained by nucleophilic attack of A^- or A^- on a suitable electrophile BX; in many cases it is not clear whether

³⁶ E. Hobolth and H. Lund, *Acta Chem. Scand., Ser. B* **B30**, 895 (1976).

³⁷ H. Lund and L. H. Kristensen, *Acta Chem. Scand., Ser. B* **B33**, 495 (1979).

³⁸ P. Martigny and J. Simonet, *J. Electroanal. Chem.* **81**, 407 (1977).

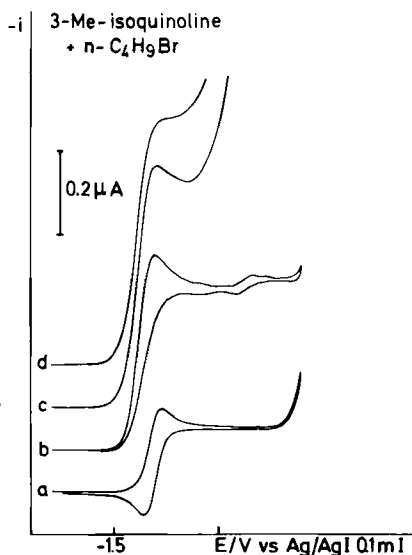
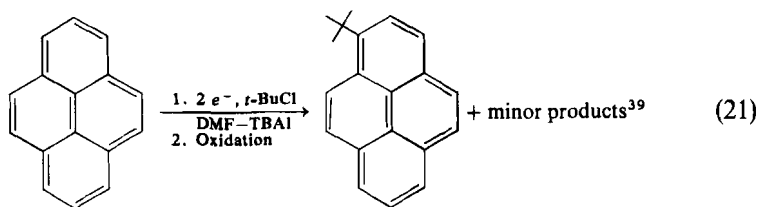


Fig 7. Cyclic voltammograms in DMF of 3-methylisoquinoline in the absence (a) and presence (b, c, and d) of increasing concentrations of butyl bromide, $v = 10 \text{ mV sec}^{-1}$. (Reprinted from Ref. 25 with permission from Elsevier Sequoia S.A.)

an S_N2 reaction is operating or whether the reaction is initiated by a one-electron transfer. Knowledge of the redox potentials of the compounds involved is necessary in order to judge whether an electron-transfer reaction is a likely pathway; some reactions of the latter type will be discussed below.

Electrophiles may be alkylating and acylating agents and CO_2 . Tertiary alkyl halides couple more efficiently than primary. The following examples illustrate the scope.³⁹⁻⁵⁵

- ³⁹ P. E. Hansen, A. Berg, and H. Lund, *Acta Chem. Scand., Ser. B* **B30**, 267 (1976).
- ⁴⁰ C. Degrand and H. Lund, *Acta Chem. Scand., Ser. B* **B31**, 593 (1977).
- ⁴¹ U. Hess, D. Huhn, and H. Lund, *Acta Chem. Scand., Ser. B* **B34**, 413 (1980).
- ⁴² E. Hobolth and H. Lund, *Acta Chem. Scand., Ser. B* **B31**, 395 (1977).
- ⁴³ C. Degrand and H. Lund, *Nouv. J. Chim.* **1**, 35 (1977).
- ⁴⁴ H. Lund and C. Degrand, *C. R. Acad. Sci., Ser. C* **287**, 535 (1978).
- ⁴⁵ T. Shono, I. Nishiguchi, and H. Ohmizu, *Chem. Lett.*, 1021 (1977).
- ⁴⁶ T. Shono, I. Nishiguchi, and H. Ohmizu, *J. Am. Chem. Soc.* **99**, 7396 (1977).
- ⁴⁷ H. Lund, *Acta Chem. Scand., Ser. B* **B31**, 424 (1977).
- ⁴⁸ H. Lund and C. Degrand, *Tetrahedron Lett.*, 3593 (1977).
- ⁴⁹ H. Lund and C. Degrand, *Acta Chem. Scand., Ser. B* **B33**, 424 (1979).
- ⁵⁰ S. Wawzonek and A. Gundersen, *J. Electrochem. Soc.* **107**, 537 (1960); **111**, 324 (1964).
- ⁵¹ S. Wawzonek and D. Wearing, *J. Am. Chem. Soc.* **81**, 2057 (1959).
- ⁵² N. L. Weinberg, A. K. Hoffmann, and T. B. Reddy, *Tetrahedron Lett.*, 2271 (1971).
- ⁵³ D. A. Tyssee, J. H. Wagenknecht, M. M. Baizer, and J. L. Chruma, *Tetrahedron Lett.*, 4809 (1972).
- ⁵⁴ D. A. Tyssee and M. M. Baizer, *J. Org. Chem.* **39**, 2819, 2823 (1974).
- ⁵⁵ E. Lamy, L. Nadjio, and J. M. Savéant, *Nouv. J. Chim.* **3**, 21 (1979).

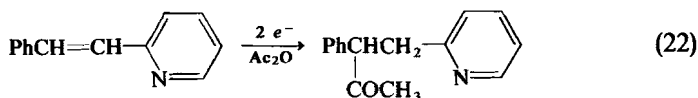


Similarly, isoquinoline may be *tert*-butylated⁴⁰ to 6-*tert*-butyl-5,6-dihydroisoquinoline or adamantylated.⁴¹ Anthracene may be reductively coupled with 1,2-dichloroethane to 9,10-dihydro-9,10-ethanoanthracene⁴² and with 1,3-dibromopropane to 2,3,3a,11b-tetrahydrocyclopentano[*a*]anthracene, and activated olefins may be *tert*-butylated.^{43,44}

Alkylation of anions is generally described by the classical S_N1 and S_N2 reactions. In some cases these reaction types are not appropriate and the reaction is better described as an electron-transfer reaction followed by a radical coupling within a solvent cage³⁷ (see Section IV,A).

4. Acylations

The electrochemical acylation reaction⁴⁵⁻⁴⁹ produces the equivalent of R $\dot{\text{C}}=\text{O}$, which (formally) couples with the substrate. In some cases the substrate is reduced to its anion-radical which might transfer an electron to the acylation agent, and in other cases the acylating agent is reduced. Activated olefins are attacked at the site where a Michael addition would have taken place [Eq. (22)]. Aromatic rings with low resonance energy may be attacked similarly.⁴⁷



5. Carboxylations

Carboxylation^{16,50-55} of anion-radicals is usually best described as a nucleophilic attack on CO₂, but in some cases electron transfer takes place.^{24,55}

6. Other Reactions

Among other electron-transfer coupling and substitution reactions may be mentioned the reduction of disulfides in the presence of O₂ leading to sulfinic

acids,⁵⁶ oxidations with electrogenerated superoxide ions $O_2^{\cdot-}$,⁵⁷ and the electrochemically induced $S_{RN}1$ reactions.^{58,59} A number of rearrangements are induced by electron transfer,⁶⁰⁻⁶² and polymerization reactions^{63,64} may be initiated by electrochemically generated radicals or radical ions.

III. Electrolytic Formation of Heterocyclic Systems

Section III contains a discussion of the electrolytic reactions in which a heterocyclic system is formed; the reactions will be treated under the following headings: ring formation reactions, ring contractions, and ring expansions.

A. RING-FORMATION REACTIONS

In the electrolytic formation of heterocyclic systems the role of the current is to bring one or both of the reaction centers to a suitable oxidation state. These reactions may be classified in different ways; here they are treated according to the type of bond formed.

1. Formation of Carbon-Nitrogen Bonds

a. *By Reductive Intramolecular Ring Closure.* Lund¹ described a number of ring-closure reactions in which a nitro group was reduced to a hydroxylamino or amino group, and the nucleophile thus formed reacted with an electrophilic center such as a carbonyl group, a carboxylic acid derivative, or a nitrile group. If a five-membered or larger ring could be formed by attack of the nitrogen, then the nitrogen in the hydroxylamino group acted as a nucleophile. The oxygen was the attacking group when the nitro group and the electrophilic center were at vicinal carbon atoms [Eq. (23)].

⁵⁶ C. Degrand and H. Lund, *Acta Chem. Scand., Ser. B* **B33**, 512 (1979).

⁵⁷ H. Sagae, M. Fujihira, H. Lund, and T. Osa, *Heterocycles* **13**, 321 (1979).

⁵⁸ J. Pinson and J. M. Savéant, *J. Am. Chem. Soc.* **100**, 1506 (1978).

⁵⁹ J. M. Savéant, *Acc. Chem. Res.* **13**, 323 (1980).

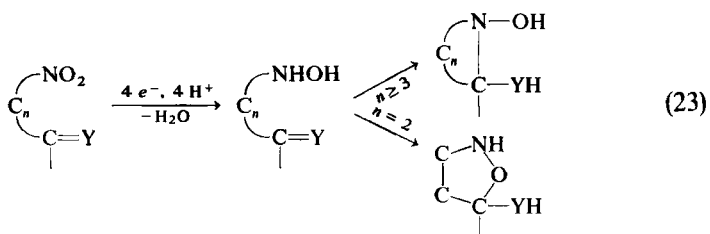
⁶⁰ K. Kistenbrügger, C.-P. Klages, and J. Voss, *J. Chem. Res., Synop.*, 320 (1979).

⁶¹ K. Praefcke, C. Weichsel, M. Falsig, and H. Lund, *Acta Chem. Scand., Ser. B* **B34**, 403 (1980).

⁶² L. Cedheim and L. Eberson, *Acta Chem. Scand., Ser. B* **B30**, 527 (1976).

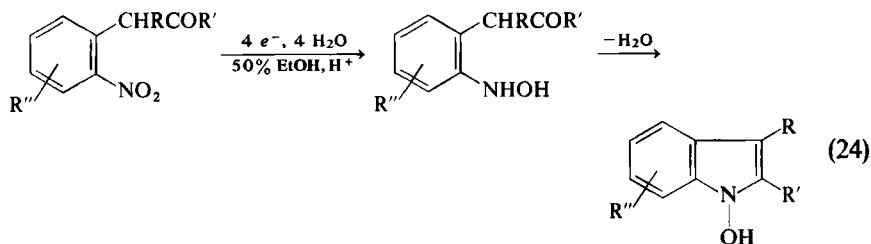
⁶³ S. N. Bhadani and G. Parravano, in "Organic Electrochemistry" (M. M. Baizer and H. Lund, eds.), Chapter 31. Dekker, New York, 1983.

⁶⁴ B. L. Funt and J. Tanner, *Tech. Chem. (N.Y.)* **5**, Part 2, 559 (1975).

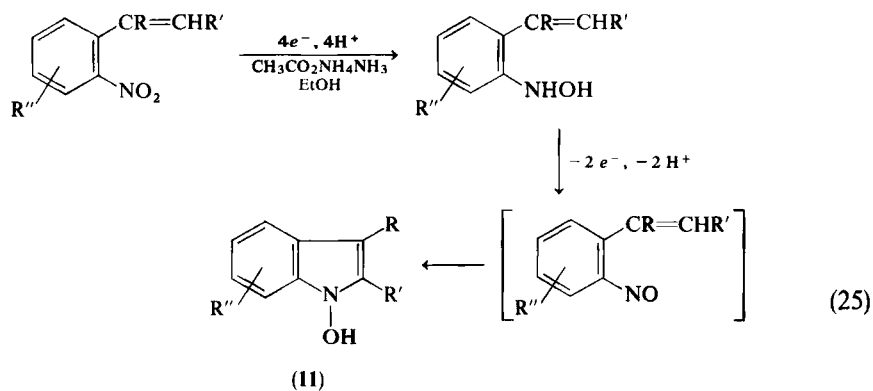


Below are some examples published since 1969.

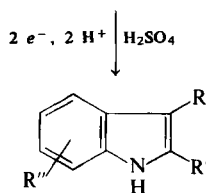
N-Hydroxyindols (11) have been prepared in two ways,⁶⁵ [Eqs. (24) and (25)]. Equation (25) is a variation in which the hydroxylamino group is oxidized to a nitroso group, which then adds to a C=C bond. In acidic solution the *N*-hydroxy group can be reductively removed.



(11)

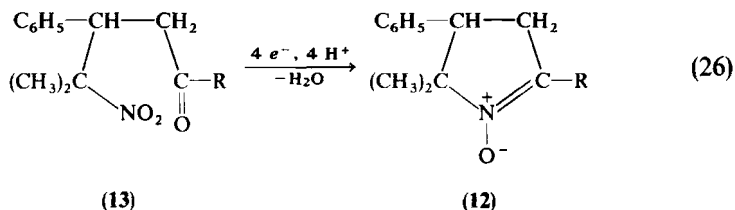


(11)

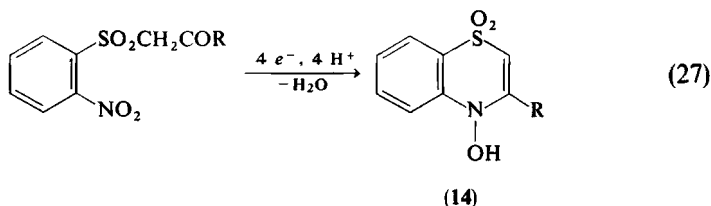


⁶⁵ R. Hazard and A. Tallec, *Bull. Soc. Chim. Fr.*, 3040 (1973); 121 (1974).

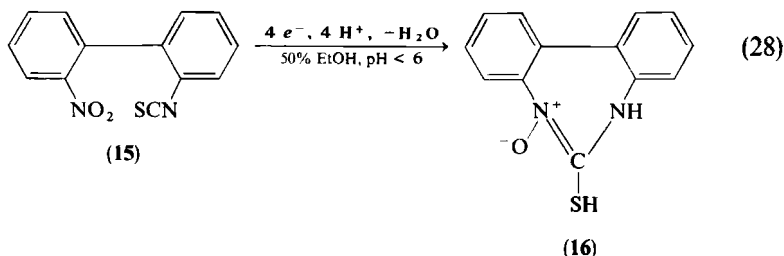
Similarly, pyrroline *N*-oxides (12), pyrrolines, or pyrrolidines can be prepared from γ -nitro ketones (13) in aqueous organic media; at low temperatures the pyrroline *N*-oxide is obtained⁶⁶ [Eq. (26)].



Reduction of $\text{O}_2\text{NC}_6\text{H}_4\text{SO}_2\text{CH}_2\text{COR}$ under analogous conditions gave 3-substituted 4-hydroxy-4*H*-1,4-benzothiazine 1,1-dioxide (14) [Eq. (27)].⁶⁷



A six-membered ring is formed in the reduction of 2-nitrophenyl-2'-carboxylic acid⁶⁸ or 6,6'-dinitrophenyl-2,2'-dicarboxylic acid.⁶⁹ In the former case a phenanthridine is formed, in the latter a 4,9-diazapyrene. Similarly, a seven-membered ring is obtained when 2-nitro-2'-isothiocyanobiphenyl (15) is reduced in acidic solution with the formation of 6-mercaptodibenzo[*d,f*]-1,3-diazepine 3-oxide (16)⁷⁰ [Eq. (28)].



⁶⁶ M. Carion, R. Hazard, M. Jubault, and A. Tallec, *Tetrahedron Lett.* **22**, 3964 (1981).

⁶⁷ C. P. Maschmeyer, H. Tanneberg, and H. Matschiner, *Z. Chem.* **21**, 219 (1981).

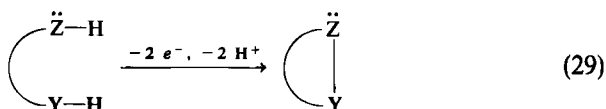
⁶⁸ J. Hlavaty, J. Volke, O. Manousek, and V. Bakos, *Electrochim. Acta* **24**, 541 (1979).

⁶⁹ E. Yu. Khmel'nitskaya, E. A. Zalogina, G. I. Migachev, and A. M. Andrievskii, *Zh. Obshch. Khim.* **47**, 2603 (1977) [*CA* **88**, 81028 (1978)].

⁷⁰ J. Hlavaty, J. Volke, and O. Manousek, *J. Electroanal. Chem.* **61**, 219 (1975).

Four-membered rings are not obtained during reduction of α -nitro- β -keto alkenes; the oxygen of the hydroxylamine intermediate attacks the electrophilic center^{1,71} with formation of isoxazole derivatives.

b. *By Oxidative Intramolecular Ring Closure.* Oxidative ring closure is the result of intramolecular attack by a nucleophilic center in the molecule at the site of oxidation initiated anodically. That site can be a free radical, a radical-cation, or a cation center, and ring closure to such sites is an intramolecular addition process. Most intramolecular cyclizations ($\text{RH}_2 \rightarrow \text{cR}$) are two-electron overall exchange reactions occurring along a single voltammetric wave [Eq. (29)].



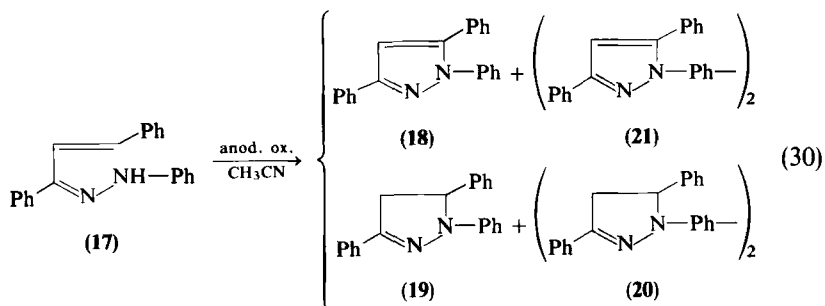
Cyclic voltammetry (Section II,A) and other electroanalytical techniques⁹ may give answers to the following questions: (i) in which stage does the cyclization occur, e.g., in the stage of a radical-cation or dication, (ii) which is the rate-determining step, (iii) what is the sequence of the reactions in the overall conversion ($\text{RH}_2 \rightarrow \text{cR}$)? The second electron is very commonly transferred through a disproportionation of the intermediate radical or radical-cation.

Intermolecular anodic cyclizations often involve initial coupling of radical-cations followed by a chemical cyclization reaction. An alternative is cyclization by internal nucleophilic addition of some reactant to an intermediate derived by anodic oxidation.

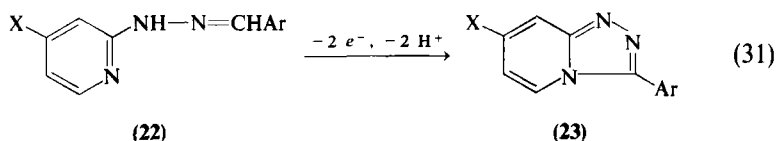
Many examples of ring closures by oxidation of hydrazone derivatives have been reported. Anodic oxidation of chalcone⁷² phenylhydrazone (17) performed in $\text{CH}_3\text{CN}-\text{LiClO}_4$ at platinum, using controlled potential electrolysis, gave 1,3,5-triphenylpyrazole (15–40% yield) (18), 1,3,5-triphenyl- Δ^2 -pyrazoline (19), 1,3,5-triphenyl- Δ^2 -pyrazolinium perchlorate, 4,4-bis[3,5-diphenyl- Δ^2 -pyrazolinyl-(1)]-biphenyl (20), the diperchlorate of 20, and 4,4'-bis-[3,5-diphenylpyrazolyl-(1)]-biphenyl (21) [Eq. (30)].

⁷¹ C. Bellec, D. Bertin, R. Colau, S. Deswarte, P. Maitte, and C. Viel, *J. Heterocycl. Chem.* **16**, 1611, 1657 (1979).

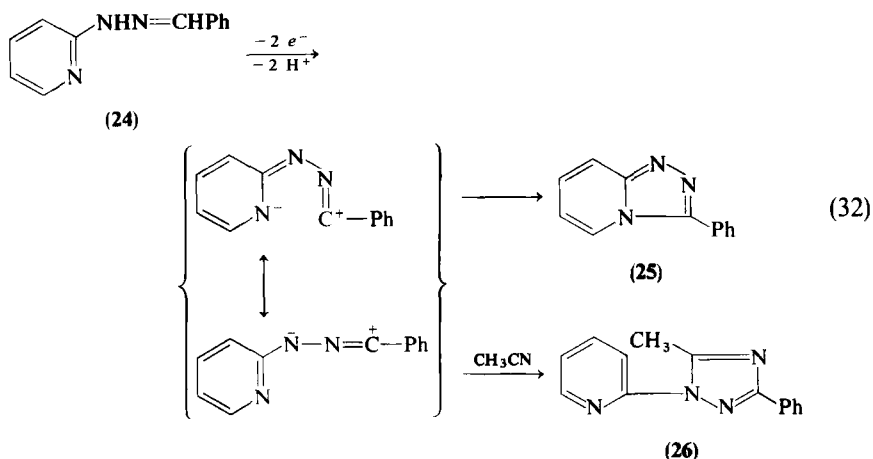
⁷² I. Tabaković, M. Laćan, and Sh. Damoni, *Electrochim. Acta* **21**, 621 (1976).



Several heterocyclic hydrazones (22) have been oxidized in $\text{CH}_3\text{CN}-\text{Et}_4\text{NClO}_4$ solution with addition of 60% HClO_4 to *s*-triazolo[4,3-*a*]pyridine (23) derivatives in yields ranging from 55 to 92%⁷³ [Eq. (31)].

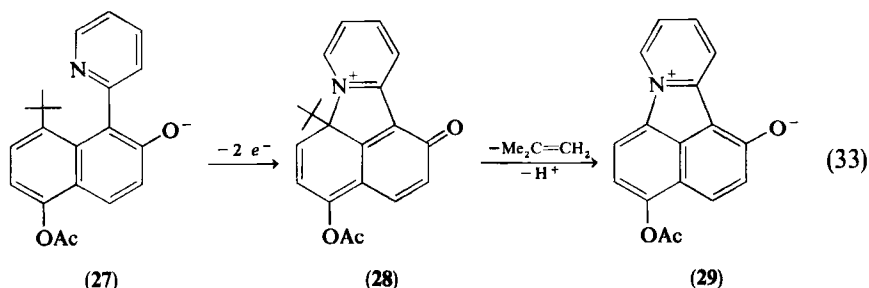


The oxidative cyclization is presumed to occur after the second electron transfer and to involve a nitrilimine as an intermediate. When benzylidene 2-pyridylhydrazone (24) was oxidized, 3-phenyl-3-triazolo[4,3-*a*]pyridine (25) was isolated as well as 1-(2-pyridyl)-3-phenyl-5-methyl-1,2,4-triazole (26). Presumably, the intermediate nitrilimine may either react with acetonitrile in a 1,3-dipolar cycloaddition reaction or cyclize as a 1,5-dipolar species, according to Eq. (32).



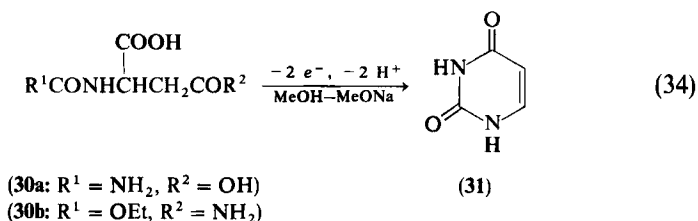
⁷³ S. Crljenak, I. Tabaković, D. Jeremić, and I. Gaon, *Acta Chem. Scand., Ser. B* **B37**, 527 (1983).

A special case of an intramolecular nucleophilic reaction on the sterically hindered anion of 5-acetoxy-8-*tert*-butyl-2-hydroxy-1-(2-pyridyl)naphthalene (**27**) was performed by anodic oxidation.⁷⁴ The product is the isolable perchlorate **28**, which slowly loses isobutylene to give the zwitterion **29** [Eq. (33)].



The initial attack in the anodic oxidation of papaverine⁷⁵ probably involves a similar attack; further oxidation and dimerization leads to the isolated product, 12,12'-bis-(2,3,9,10-tetramethoxyindolo[2,1-*a*])isoquinólyl. The electrooxidation of a tetramethoxy substituted 2-methyl-1-phenethyl-1,2,3,4-tetrahydroisoquinoline to a dibenzoquinolizinium derivative is analogous.⁷⁶

An interesting transformation of carbamoylaspartic acid (**30a**) or ethoxycarbonylasparagine (**30b**) to uracil (**31**) was performed by electrochemical oxidative decarboxylation.⁷⁷ The same ring-closure reaction occurs in a biological system via an enzyme-catalyzed oxidation. Good yields and mild conditions of the electrochemical transformations give promise of wide application [Eq. (34)].



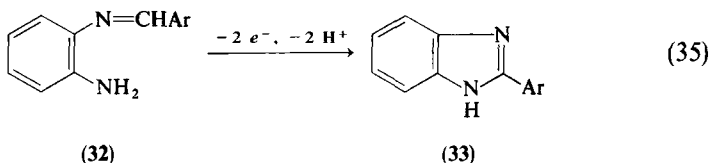
⁷⁴ G. Popp, *J. Org. Chem.* **37**, 3058 (1972).

⁷⁵ U. Hess, K. Hiller, R. Schroeder, and E. Gründemann, *J. Prakt. Chem.* **319**, 568 (1977).

⁷⁶ A. Najafi and M. Sainsburg, *Heterocycles* **6**, 459 (1977).

⁷⁷ T. Iwasaki, H. Horikawa, K. Matsumoto, and M. Miyoski, *Tetrahedron Lett.*, 4799 (1978).

Several examples of oxidative ring closures by attack on an azomethine group by an amine have been reported⁷⁸; thus arylidene-*o*-phenylenediamines (**32**) have been oxidized to 2-arylbenzimidazoles (**33**) [Eq. (35)].



The reaction was carried out in $\text{CH}_3\text{CN}-\text{Et}_4\text{NClO}_4$ with addition of pyridine as base, using controlled potential electrolysis and a divided cell. The yield of (**33**) varied greatly, depending on the method of electrolysis. Oxidation of **32** in the presence of pyridine gave **33** in 60–85% yield, whereas the electrolysis without pyridine lowered the yield to 10–20%, and products of hydrolysis, because of accumulation of the acid in the anodic compartment, were identified. The mechanism of the reaction proposed on the basis of electroanalytical results involves the cyclization of the radical-cation or its deprotonation as the rate-determining step.⁷⁸

N-Hydroxyindoles have been prepared by controlled-potential oxidation of some 2-(*o*-hydroxylaminophenyl) alkenes in slightly basic media.⁶⁵

c. *By Reductive Intermolecular Reactions.* Electrochemical reductive alkylation^{23–26} and acylation^{45–49} are now well-established methods (Section II,B); the alkylating or acylating agent reacts with either the substrate anion-radical or the mono- or dianion of the dihydro compound. This reaction has also been employed for the formation of heterocyclic compounds by employing, α,ω -dihalo alkanes,^{79,80} ω -haloacid chlorides, or acid chlorides of dicarboxylic acids.^{81–84} Azobenzenes, nitrobenzenes, and azomethine compounds have been used as substrates [Eqs. (36)–(39)].

⁷⁸ M. Laćan, V. Rogić, I. Tabaković, D. Galijaš, and T. Solomun, *Electrochim. Acta* **28**, 199 (1983).

⁷⁹ T. Troll and W. Elbe, *Electrochim. Acta* **22**, 615 (1977).

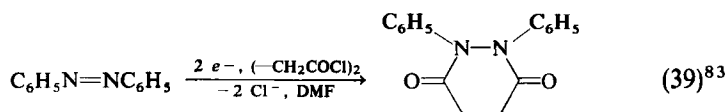
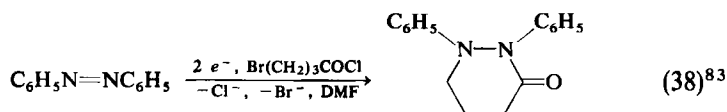
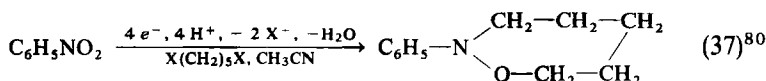
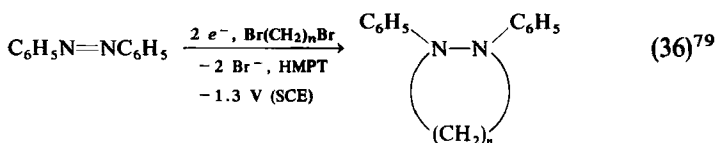
⁸⁰ J. H. Wagenknecht, *J. Org. Chem.* **42**, 1836 (1977).

⁸¹ C. Degrand, G. Grosdemouge, and P.-L. Compagnon, *Tetrahedron Lett.*, 3023 (1978).

⁸² C. Degrand and D. Jacquin, *Tetrahedron Lett.*, 4955 (1978).

⁸³ C. Degrand, P.-L. Compagnon, G. Belot, and D. Jacquin, *J. Org. Chem.* **45**, 1189 (1980).

⁸⁴ C. Degrand, G. Belot, F. Gasques, and P.-L. Compagnon, *Electrochim. Acta* **27**, 1529 (1982).

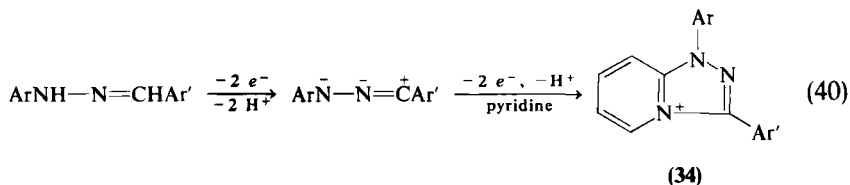


The reaction requires a very dry medium, otherwise the anionic intermediates are protonated and thus not alkylated or acylated. It may be necessary to remove the last traces of proton donors by passing the medium through a column of very active alumina.

Other experimental conditions can be important.⁸⁴ Thus the electroreductive coupling between 4-chlorobutyl chloride and nitrosobenzene to 2-phenyltetrahydro-2H-1,2-oxazine-3-one gives low yields in DMF at room temperature. An acceptable yield is obtained in acetonitrile at room temperature, still more at -18°C . The lower yield obtained using DMF is due mainly to a higher reactivity of the electrophile, which forms an immonium salt with DMF.

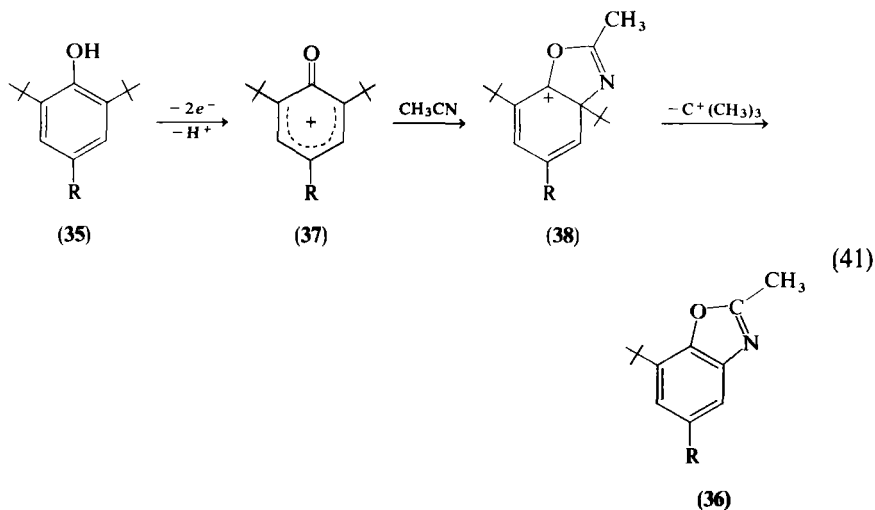
d. *By Oxidative Intermolecular Reaction.* An intermolecular ring formation takes place in the synthesis of s-triazolo[4,3-a]pyridinium salts (34) by anodic oxidation of an aldehyde hydrazone in the presence of pyridine.⁸⁵ The initially formed nitrilimine is attacked by pyridine; this is followed by a nucleophilic attack on the pyridinium ring and further oxidation [Eq. (40)].

⁸⁵ I. Tabaković and S. Crljenak, *Heterocycles* **16**, 699 (1981).



The electrochemical generation of a nitrilimine provides an entrance to a wide range of heterocyclic systems via anodic oxidation of aldehyde hydrazones. The same reaction was used for annelation of various heterocyclic systems,⁸⁶ e.g., substituted pyridines, quinolines, isoquinolines, indoles, imidazoles, benzimidazoles, and benzotriazoles.

Anodic oxidation of 2,6-di-*tert*-butylphenols (35) in acetonitrile or acetonitrile-perchloric acid leads to 7-*tert*-butyl-2-methylbenzoxazoles (36). In the absence of nucleophiles, the initially formed cation 37 adds acetonitrile to give 38, which loses a *tert*-butyl cation, [Eq. (41)].⁸⁷

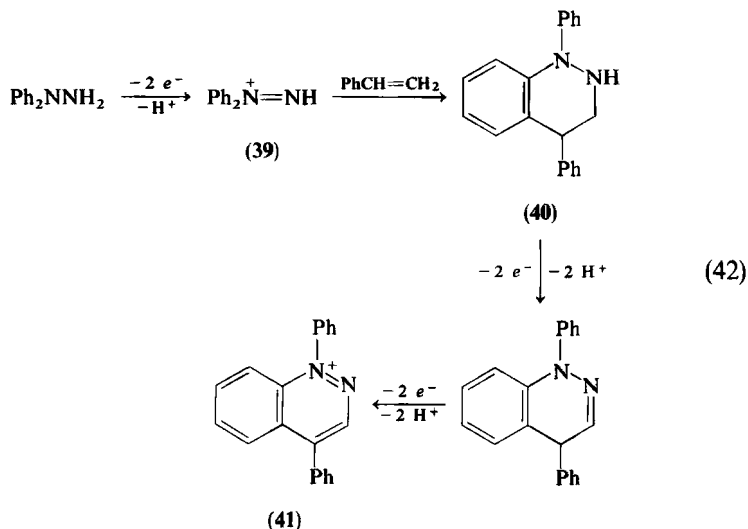


Anodic oxidation of 1,1-diphenylhydrazine in neutral acetonitrile gives a relatively stable diphenyldiazonium ion 39, which may add to styrene in the

⁸⁶ I. Tabaković and S. Crljenak, *Ext. Abstr. 10th Sandbjerg Meet. Org. Electrochem.*, 1982, 45 (1982).

⁸⁷ E.-L. Dreher, J. Bracht, M. El-Mobayed, P. Hütter, W. Winter, and A. Rieker, *Chem. Ber.* 115, 288 (1982).

presence of acid, giving 1,4-diphenyl-1,2,3,4-tetrahydrocinnoline **40**. Anodic oxidation of 1,1-diphenylhydrazine at a higher potential in acidic acetonitrile containing excess styrene led to the 1,4-diphenylcinnolinium ion **41**,⁸⁸ which may be reduced reversibly to the corresponding radical, [Eq. (42)].



Structurally different hydrazine derivatives reacted similarly⁸⁸⁻⁹³ in the presence of various olefins. There are exceptions. Some olefins are unreactive. Cyclohexene gives rise to a quite different reaction, which involves acetonitrile as a solvent. The reaction with 2-butenes does not give a heterocyclic product.⁹⁴ The action of triethylamine on a solution of the electrochemically prepared 1,1-dimethyl- or 1,1-dibenzyl-2-(2,4-dinitrophenyl)diazonium cations gives the corresponding azomethine-imine 1,3-dipoles (**42**) by deprotonation of the alkyl group. These too react with electron-rich, but not with electron-poor double bonds, giving rise to pyrazolidine (**43**) derivatives in a concerted and regioselective fashion⁹⁵ [Eq. (43)].

⁸⁸ G. Cauquis and M. Genies, *Tetrahedron Lett.*, 3403 (1970).

⁸⁹ G. Cauquis and M. Genies, *Tetrahedron Lett.*, 3959 (1971).

⁹⁰ G. Cauquis, B. Chabaud, and M. Genies, *Tetrahedron Lett.*, 2389 (1974).

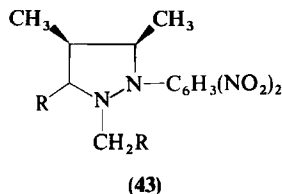
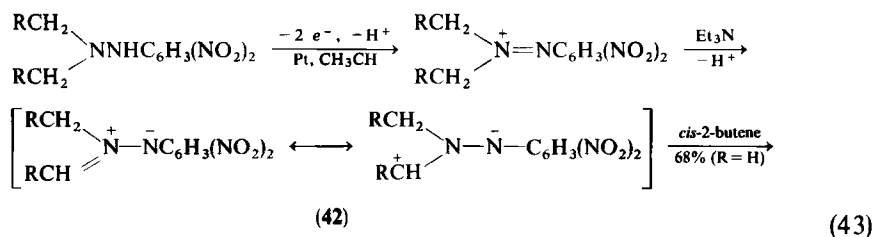
⁹¹ G. Cauquis, B. Chabaud, and M. Genies, *Bull. Soc. Chim. Fr.*, 583 (1975).

⁹² G. Cauquis, B. Chabaud, and M. Genies, *Tetrahedron Lett.*, 2583 (1977).

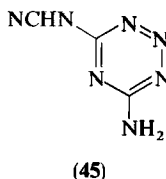
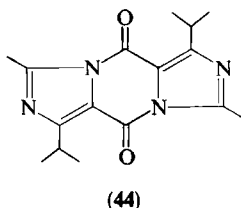
⁹³ G. Cauquis and G. Riverdy, *Tetrahedron Lett.*, 3267 (1977).

⁹⁴ G. Cauquis, B. Chabaud, and M. Genies, *Bull. Soc. Chim. Fr.*, 3487 (1973).

⁹⁵ G. Cauquis and B. Chabaud, *Tetrahedron* **34**, 903 (1978).



On anodic oxidation of 3,6-diisobutylpiperazine-2,5-dione in acetonitrile, a compound was obtained, which was suggested to be 1,6-diisopropyl-3,8-dimethyl-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-5,10-dione (44), formed by 1,3-cycloaddition of a primary oxidation product to the solvent.⁹⁶ Another heterocyclic synthesis by intermolecular coupling of 2,4,5-tri-*tert*-butylphenol with acetonitrile has been reported.⁹⁷



The electrochemical oxidation of isobutyraldehyde⁹⁸ and acetaldehyde⁹⁹ in methanol-ammonia, containing lithium chloride, yields *s*-triazines through formation of an iminomethoxy adduct, $\text{RC}(=\text{NH})\text{OCH}_3$, followed by trimerization with liberation of methanol. No *s*-triazine is obtained from formalin, and benzaldehyde gives only a 1% yield of *s*-triazine. Cyanamide has also been oxidized at a platinum anode in aqueous potassium hydroxide.¹⁰⁰ The oxidation products consisted of several known products,

⁹⁶ L. A. Simonson and C. K. Mann, *Tetrahedron Lett.*, 3303 (1970).

⁹⁷ G. Popp and N. C. Reitz, *J. Org. Chem.* **37**, 3646 (1972).

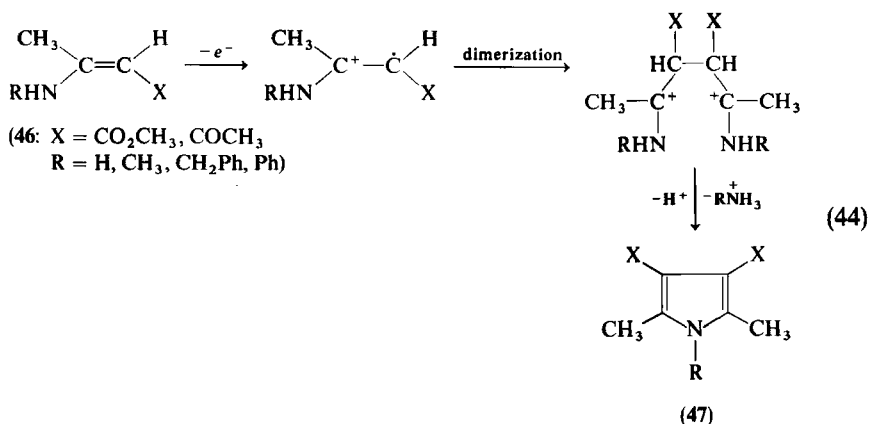
⁹⁸ B. F. Becker and H. P. Fritz, *Chem. Ber.* **108**, 3292 (1975).

⁹⁹ B. F. Becker and H. P. Fritz, *Chem. Ber.* **109**, 1346 (1976).

¹⁰⁰ K. Kubo, T. Nonaka, and K. Odo, *Bull. Chem. Soc. Jpn.* **49**, 1339 (1976).

e.g., dicyanoimine, cyanourea, and dicyanodiamide, together with new compounds with the rare 1,2,3,5-tetrazine ring, such as 4-amino-6-cyanamino-1,2,3,5-tetrazine (**45**) and 4-ureido-6-cyanoguanidino-1,2,3,5-tetrazine. The structures of the new compounds were determined from spectral data and the decomposition products obtained on heating them in dilute mineral acid.

Anodic oxidation of enamine ketones or esters in $\text{CH}_3\text{OH}-\text{NaClO}_4$ at a graphite anode gives substituted pyrroles in 15–45% yield.¹⁰¹ Formation of the symmetrically substituted pyrroles **47** indicated radical dimerization of radical-cations formed as primary products from **46**. This process leads to dications from which the pyrroles can be formed by cyclization and elimination of an amine [Eq. (44)].



Similarly, the anodic dimerization of styrene in $\text{CH}_3\text{CN}-\text{H}_2\text{O}-\text{Et}_4\text{N}-\text{pTS}$ proceeds via an intermediate cation and its deprotonation or solvolysis with the formation of substituted 1,4-butanediols, tetrahydrofurans, tetrahydropyrroles, and some other products depending on the experimental conditions.¹⁰²

Oxidation of conjugated dienes in $\text{CH}_3\text{CN}-\text{NaClO}_4$ in the presence of 1,3-dimethylurea gives a mixture of the possible 4,5-disubstituted 1,3-dimethylimidazolidin-2-ones in about 40% yield.¹⁰³ Anodic oxidation of 2,4-hexadiene, 1,3-butadiene, and 1,3-cyclohexadiene in $\text{CH}_3\text{CN}-\text{H}_2\text{O}-\text{NaClO}_4$ yields diols, 2-oxazolines, and 3-pyrrolines.¹⁰⁴ The product distribution is influenced by the supporting electrolyte.

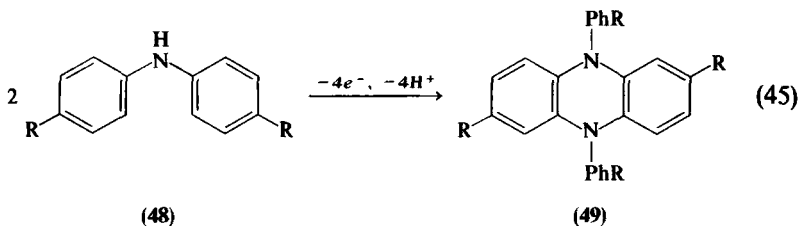
¹⁰¹ D. Koch and H. J. Schäfer, *Angew. Chem.* **85**, 264 (1973).

¹⁰² E. Steckhan and H. J. Schäfer, *Angew. Chem.* **86**, 472 (1974).

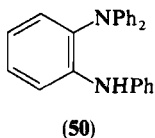
¹⁰³ H. Baltes, L. Stork, and H. J. Schäfer, *Angew. Chem.* **89**, 425 (1977).

¹⁰⁴ H. Baltes, L. Stork, and H. J. Schäfer, *Chem. Ber.* **112**, 807 (1979).

The intermolecular oxidative cyclization of 4,4'-disubstituted diphenylamines (48) to form the corresponding diarylphenazines (49) occurs both chemically^{105,106} and electrochemically.^{107,108} The overall process is as shown in [Eq. (45)].



The mechanism of the reaction that occurs at a platinum anode in $\text{CH}_3\text{CN}-\text{Et}_4\text{NClO}_4$ has been elucidated by showing that *N,N,N*-triphenyl-*o*-phenylenediamine (50) is oxidized quantitatively at +1.3 V versus SCE to give the dication of (49), which then can be reduced to 49 at -0.7 V versus SCE. Selection rules for the conversion of diphenylamines to dihydrophenazines are given.¹⁰⁹



Thus although an *o*-phenylenediamine cannot be detected during the oxidation of diphenylamine, it is probably an intermediate. A new compound, 5,12-di-2-naphthylidibenzo[*c,j*]phenazine, was found to be produced, according to the same mechanism, in ~30% yield by anodic oxidation of di-2-naphthylamine in $\text{CH}_3\text{CN}-\text{NaClO}_4$.¹¹⁰ A detailed study of the electrochemical oxidation of a series of *p*-monosubstituted diphenylamines¹¹¹ and *p,p'*-disubstituted diphenylamines,¹¹² giving rise to 5,10-diaryl-5,10-dihydrophenazines and other coupling products, has been published.

¹⁰⁵ H. Wieland, *Ber. Dtsch. Chem. Ges.* **41**, 3478 (1908).

¹⁰⁶ H. Wieland and H. Lecher, *Ber. Dtsch. Chem. Ges.* **45**, 2600 (1912).

¹⁰⁷ G. Cauquis, H. Delhomme, and D. Serve, *Tetrahedron Lett.*, 4113, 4649 (1971).

¹⁰⁸ G. Cauquis, H. Delhomme, and D. Serve, *Tetrahedron Lett.*, 1965 (1972).

¹⁰⁹ P. Berkenkotter and R. F. Nelson, *J. Electrochem. Soc.* **120**, 346 (1973).

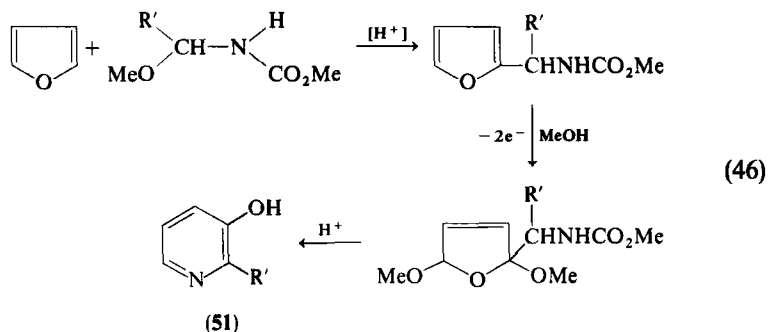
¹¹⁰ K. Yasukouchi, I. Taniguchi, H. Yamaguchi, M. Yokoyama, and M. Murasaki, *Chem. Lett.*, 1167 (1979).

¹¹¹ G. Cauquis, H. Delhomme, and D. Serve, *Electrochim. Acta* **21**, 557 (1976).

¹¹² D. Serve, *Electrochim. Acta* **21**, 1171 (1976).

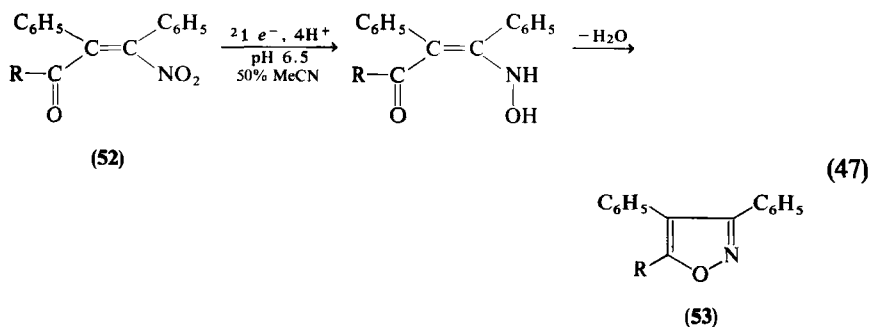
Anodic oxidation of 4'-substituted 2-nitrobenzenesulfenylanilide in CH_3CN -ethyltributylammonium trifluoromethanesulfonate, containing 1% trifluoroacetic acid and 1% trifluoroacetic anhydride, is reported to give 2,7-disubstituted phenazines in 24–56% yield.¹¹³

Urethanes can be anodically methoxylated, as other amides; they may react with furan in the presence of an acid. Anodic methoxylation of the furan gives a dimethoxydihydrofuran in the Clauson-Kaas reaction¹; on acid hydrolysis 3-hydroxypyridines (**51**) are obtained¹¹⁴ [Eq. (46)].



2. Formation of Carbon–Oxygen Bonds

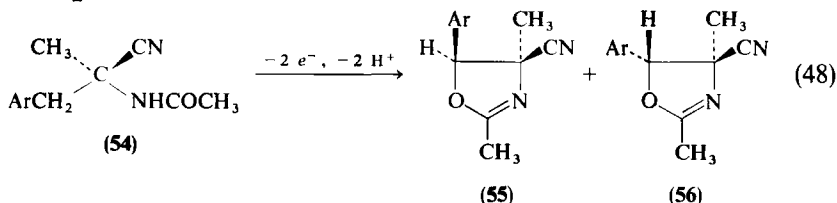
a. *By Reduction.* A carbon–oxygen bond may be formed during the reduction of nitro compounds when the nitro group and the electrophilic center are at vicinal atoms; steric conditions favor an attack by the oxygen of the hydroxylamino group rather than by the nitrogen. Thus *Z*- α -acyl- β -nitrostilbenes (**52**) form isoxazoles (**53**) on reduction in buffered medium, and *Z*- α -cyano- β -nitrostilbenes yield 5-aminoisoxazoles⁷¹ [Eq. (47)].



¹¹³ H. Sayo, K. Mori, and T. Michida, *Chem. Pharm. Bull.* **28**, 3707 (1980).

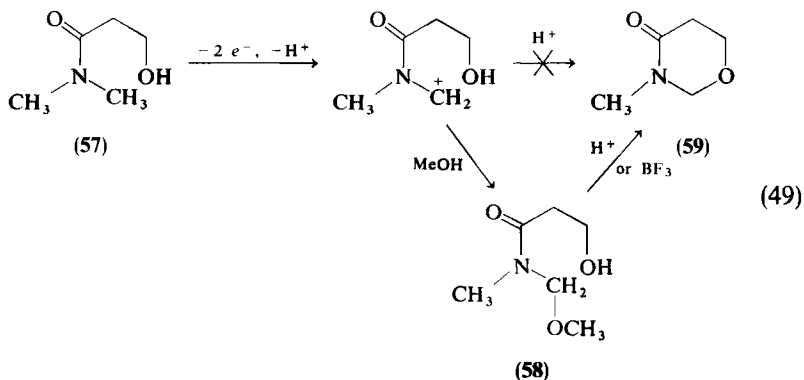
¹¹⁴ T. Shono, Y. Matsumura, K. Tsubata, and J. Takata, *Chem. Lett.*, 1121 (1981).

b. *By Oxidation.* The electron-deficient center (cation or radical-cation), formed on anodic oxidation, may react intramolecularly with an adequately located nucleophilic oxygen. An example of benzyl cation formation is the anodic oxidation of (*S*)-2-acetamido-2-(3,4-dimethoxybenzyl) propanitrile (**54**) in an AcOH–AcONa mixture, containing acetic anhydride, which leads to (4*R*,5*S*)- and (4*R*,5*R*)-4-cyano-5-(3,4-dimethoxyphenyl)-2,4-dimethyl-2-oxazoline (**55** and **56**) in a 3.5:1 ratio as the major products¹¹⁵ [Eq. (48)].



This stereoselectivity is not a result of adsorption on the electrode but stems from the nature of the benzylic cation formed as an intermediate, because the same oxazolines are formed in a similar ratio in the homogeneous reaction of **54** with $Mn(OAc)_3$.

Anodic oxidation of *N,N*-dimethyl- ω -hydroxyamides (**57**) in CH_3OH – Bu_4NBF_4 at a platinum anode leads to formation of *N*-methoxy-*N*-methyl- ω -hydroxyamides (**58**) in high yield.¹¹⁶ The latter could in some cases (formation of five-, six-, and seven-membered rings) easily be transformed to 1,3-oxaza-4-oxo heterocyclic systems (**59**) by acid catalysis [Eq. (49)]. No direct formation of the 1,3-oxazaheterocycles was observed, e.g., **57** \rightarrow **59**. An intramolecular addition of the hydroxy group to the intermediate acylammonium ion is believed to be hindered by adsorption phenomena at the anode surface.



¹¹⁵ S. H. Pines, *J. Org. Chem.* **38**, 3854 (1974).

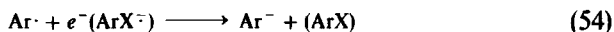
¹¹⁶ Z. Blum and K. Nyberg, *Acta Chem. Scand., Ser. B* **B36**, 165 (1982).

probably a slow, irreversible heterogeneous electron transfer, followed by a fast deprotonation leading to a neutral radical, which goes through cyclization, further oxidation, and deprotonation to the final product.

3. Formation of Carbon–Carbon Bonds

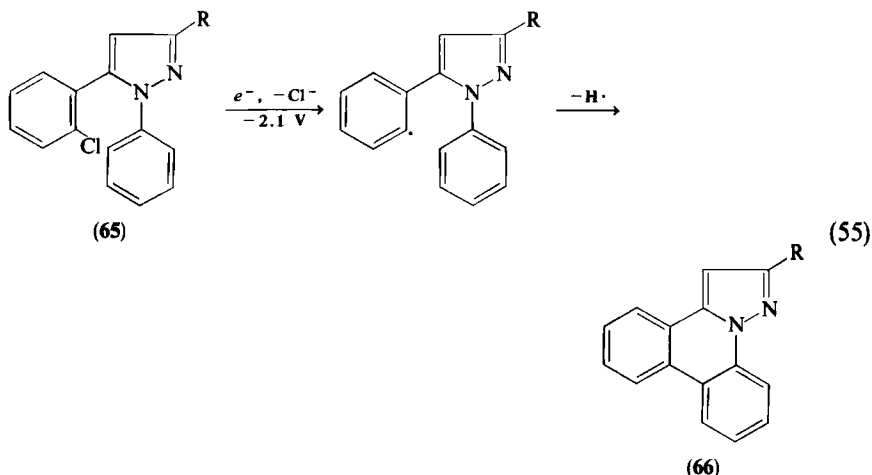
Carbon–carbon bonds may be formed both by reduction and oxidation; in the former, mostly anions or radicals are the attacking reagent; in the latter, cations or radicals.

Ring Closure Involving Radicals. Reduction of an aromatic halide goes through a radical–anion, which loses a halide ion. If the rate of this cleavage (k_2) is very high, the radical will be formed close to the electrode and will accept an electron to form a carbanion.



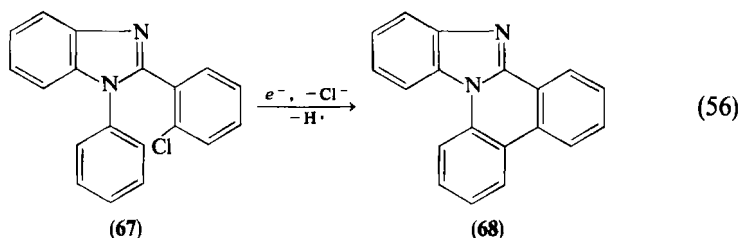
If k_2 is relatively low, the radical Ar^\cdot is formed in the bulk of the solution; it may then abstract a hydrogen atom from the solvent or other molecules, or it may add to an unsaturated system. Iodides are cleaved faster than chlorides, and bromides are cleaved at intermediate rates. For a given type of halide, the rate of cleavage is generally faster, the more negative the reduction potential.

5-(2-Chlorophenyl)-1-phenylpyrazole (**65**) affords a good yield of pyrazolo[1,5-*f*]phenanthridine (**66**) on reduction [Eq. (55)] in DMF containing

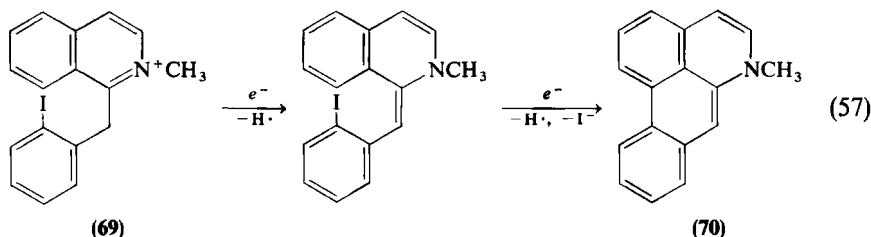


tetrapropylammonium perchlorate as supporting electrolyte¹²¹; a side reaction is the formation of a 1,5-diphenylpyrazole, which results from the intermediate σ -radical abstracting a hydrogen atom from the solvent. The scheme is consistent with the experimental findings $n = 1.15 \text{ F mol}^{-1}$.

Similarly, 2-halo-*N*-methylbenzanilides give *N*-methylphenanthridone (and other products), and 2-(2-halophenyl)imidazole or -benzimidazole derivatives (67) form imidazolo(benzimidazolo)phenanthridine derivatives (68) [Eq. (56)].¹²²⁻¹²⁵



Aporphines may be prepared through a similar ring closure. *N*-Methyl-1-(2'-iodobenzyl)isoquinolinium salts (69) can be reduced in acetonitrile¹²⁶ at a potential more negative than the second peak, according to Eq. (57). The electron consumption is 2.0 F mol^{-1} , and two hydrogen atoms are expelled during the reaction, so that the net uptake of electrons is 0. Catalytic reduction of 70 produces aporphine.



Analogous to the electrochemical reductive alkylation of ketones,¹²⁷ immonium salts may be reductively benzylated.¹²⁸ This has been used in a

¹²¹ J. Grimshaw and J. Trocha-Grimshaw, *Tetrahedron Lett.*, 993 (1974); 2601 (1975).

¹²² W. J. Begley, J. Grimshaw, and J. Trocha-Grimshaw, *J. C. S. Perkin I*, 2633 (1974).

¹²³ J. Grimshaw, R. J. Haslett, and J. Trocha-Grimshaw, *J. C. S. Perkin I*, 2448 (1977).

¹²⁴ J. Grimshaw and D. Mannus, *J. C. S. Perkin I*, 2456 (1977).

¹²⁵ J. Grimshaw, R. Hamilton, and J. Trocha-Grimshaw, *J. C. S. Perkin I*, 229 (1982).

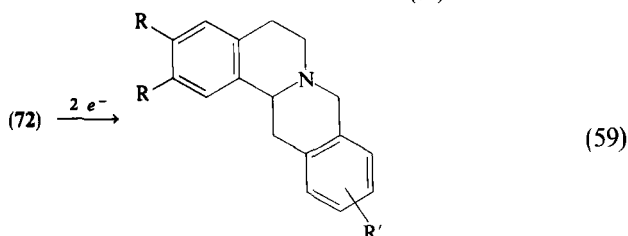
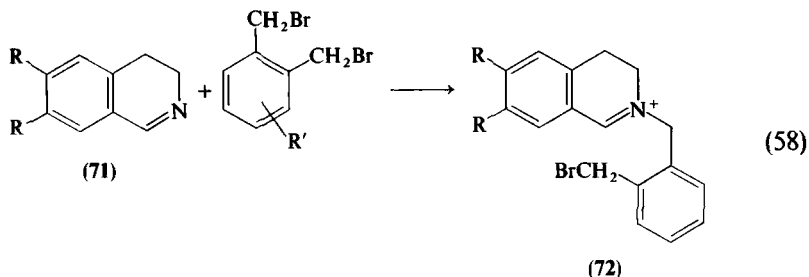
¹²⁶ R. Gottlieb and J. L. Neumeyer, *J. Am. Chem. Soc.* **98**, 7108 (1976).

¹²⁷ H. Lund and J. Simonet, *Bull. Soc. Chim. Fr.*, 1843 (1973).

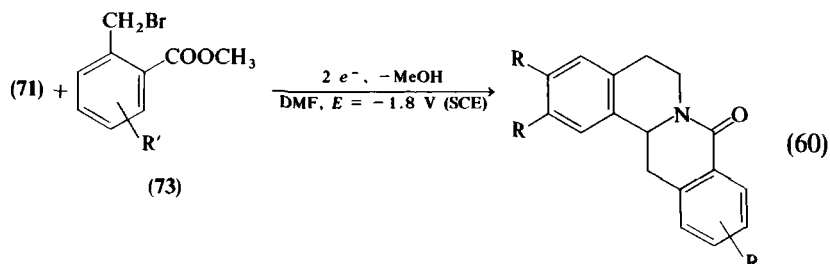
¹²⁸ T. Shono, K. Yoshida, K. Ando, Y. Usui, and H. Hamaguchi, *Tetrahedron Lett.*, 4819 (1978).

number of elegant syntheses of alkaloids. The reaction could involve an attack on the carbon–nitrogen double bond either by a benzylic radical or a benzylic anion.

A 3,4-dihydroisoquinoline (**71**) was quaternized with a derivative of α,α' -xylene dibromide to give **72** [Eq. (58)], which was then reduced with ring closure [Eq. (59)].¹²⁹



A mixture of isomers was, however, obtained if the α,α' -dibromoxylene was not symmetrical. This difficulty was overcome by using a reductive coupling of a substituted 3,4-dihydroisoquinoline (**71**) as its salt with an *o*-methoxycarbonyl-substituted benzyl bromide (**73**)¹²⁹ [Eq. (60)].

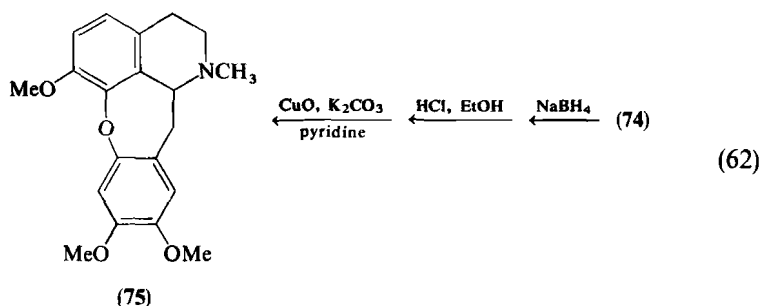
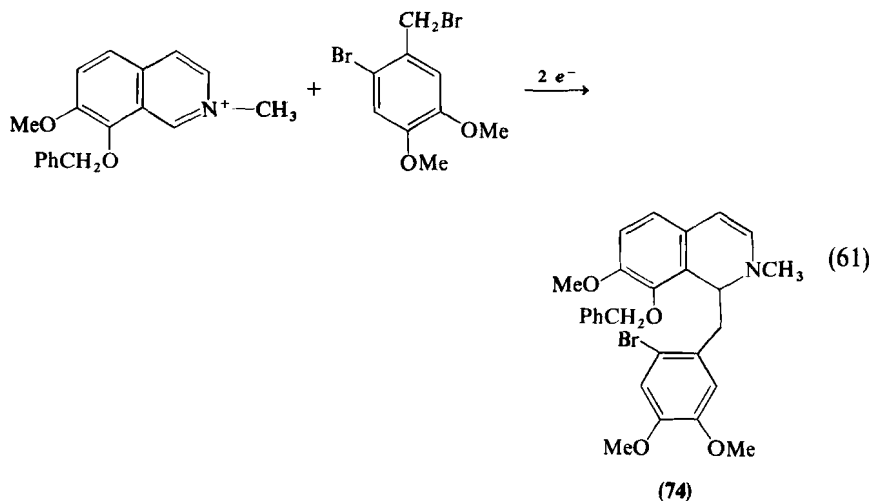


The method may be used for the synthesis of phthalide alkaloids as cordrastine by electroreductive coupling of 2-methyl-3,4-dihydro-6,7-dimethoxyisoquinolinium iodide¹³⁰ with 3-bromoconine. A further variation

¹²⁹ T. Shono, Y. Usui, T. Mizutani, and H. Hamaguchi, *Tetrahedron Lett.* **21**, 3073 (1980).

¹³⁰ T. Shono, Y. Usui, and H. Hamaguchi, *Tetrahedron Lett.* **21**, 1351 (1980).

of the reaction is the preparation of (±)-cularine (75)¹³¹ [Eqs. (61) and (62)].



Dimerization of activated olefins or ketones as a means of ring closure was mentioned in Part I; reports of more examples have been published.¹³² A special kind of coupling and ring closure occurs in the reduction of 6-phenyl-2,3-dihydrodiazepinium salt (76) in DMF to the diphenylpyrrolo-diazepine derivative (77). A plausible explanation of the formation of 77 involves dimerization of an initially formed radical, followed by intramolecular displacement of ethylenediamine.¹³³⁻¹³⁵

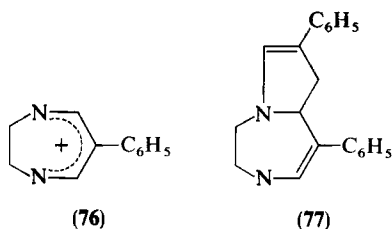
¹³¹ T. Shono, T. Miyamoto, M. Mizukami, and H. Hamaguchi, *Tetrahedron Lett.* **22**, 2385 (1981).

¹³² B. Vieth and W. Jugelt, *Z. Chem.* **21**, 286 (1981).

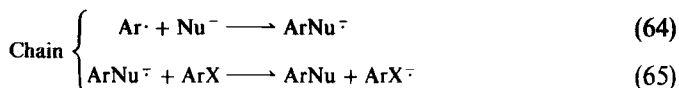
¹³³ D. Lloyd, C. A. Vincent, D. J. Walton, J. P. Declercq, G. Germain, and M. van Meerssche, *J. C. S. Chem. Commun.*, 499 (1978).

¹³⁴ D. Lloyd, C. A. Vincent, and D. J. Walton, *J. C. S. Perkin II*, 668 (1980).

¹³⁵ D. Lloyd, C. Nyns, C. A. Vincent, and D. J. Walton, *J. C. S. Perkin II*, 1441 (1980).

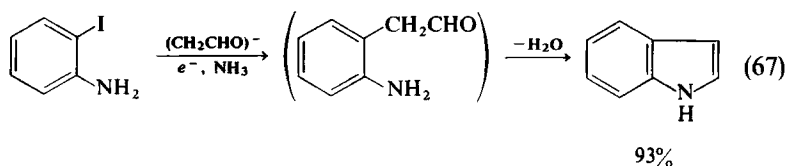


Formation of heterocyclic rings may be accomplished by electrochemically induced $S_{RN}1$ reactions^{136,137} [Eqs. (63)–(66)]. A requirement for such radical-promoted nucleophilic substitutions to proceed as a chain reaction is that the product anion-radical $ArNu^{\cdot-}$ be able to transfer an electron to the substrate [Eq. (65)]; the oxidation potential of $ArNu^{\cdot-}$ should thus be more negative than the reduction potential of ArX .



Abstraction of a hydrogen atom from the solvent HS [Eq. (66)] makes it desirable to run the reaction in a solvent that is a poor hydrogen-atom donor; liquid ammonia is a preferred solvent. Inorganic salts, such as potassium iodide or bromide, may be employed as supporting electrolyte in the $S_{RN}1$ reaction in NH_3 .

Electrostimulation of *o*-iodoaniline in the presence of enolate anions in liquid ammonia produced¹³⁸ indoles in high yield, often better than the photostimulated reactions [Eq. (67)].



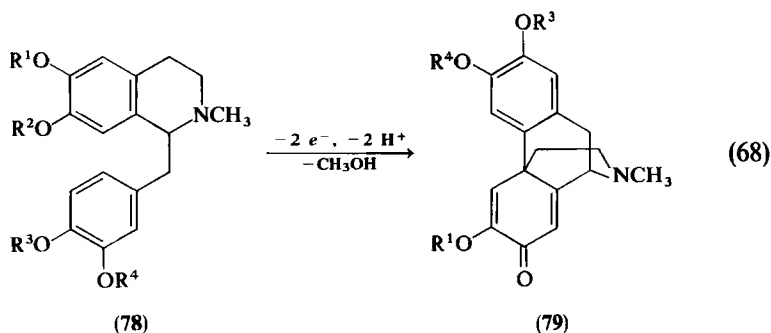
The synthetic utility of anodic reactions that couple aromatic rings activated by alkoxy groups has been explored for the formation of natural products. Thus laudanosine (**78**: $R^1 = R^2 = R^3 = R^4 = CH_3$) has been oxidized

¹³⁶ J. F. Bunnett, *Acc. Chem. Res.* **11**, 413 (1978).

¹³⁷ J. M. Savéant, *Acc. Chem. Res.* **13**, 323 (1980).

¹³⁸ K. Boujel, J. Simonet, G. Roussi, and R. Beugelmans, *Tetrahedron Lett.* **23**, 173 (1982).

at a platinum electrode in $\text{CH}_3\text{CN}-\text{Me}_4\text{NBF}_4$ to *O*-methylflavinantine (79) in 52% yield¹³⁹ [Eq. (68)].



The reaction proceeds at about 0.5 V versus $\text{Ag}-\text{Ag}^+$ by initial oxidation of the amine moiety. By complexing the amine with bis(acetonitrile)palladium(II) chloride, yields were enhanced to 63%. Similarly, *O*-benzylpseudo-codamine ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{CH}_3$; $\text{R}^4 = \text{CH}_2\text{Ph}$) has been converted to *O*-benzylflavinantine, *O*-benzylaudamine ($\text{R}^1 = \text{R}^2 = \text{R}^4 = \text{CH}_3$, $\text{R}^3 = \text{CH}_2\text{Ph}$) to *O*-benzylisoflavinantine, *O*-benzylcodamine ($\text{R}^1 = \text{R}^3 = \text{R}^4 = \text{CH}_3$, $\text{R}^2 = \text{CH}_2\text{Ph}$) to *O*-methylflavinantine, and *O*-benzylpseudolaudanine ($\text{R}^1 = \text{CH}_2\text{Ph}$, $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{CH}_3$) to 2,3-dimethoxy-6-benzylmorphinandienone in yields ranging from 43 to 63%.¹⁴⁰ When a weak acid, such as NaHCO_3 or HBF_4 , was added to the anolyte, the preparative oxidation of laudanosine gave over 90% yield of *O*-methylflavinantine.^{141,142} The mechanism of the oxidation of protonated laudanosine in acidic media^{143,144} involves a reversible electron transfer, cyclization, and deprotonation of the amine, followed by a rate-limiting electron transfer from a cyclized radical-cation to the dication. The same type of coupling has been reported during the synthesis of morphinandienone alkaloids (79) by anodic oxidation of the corresponding 1-benzyltetrahydroisoquinolines (78) in $\text{CH}_3\text{CN}-\text{HBF}_4$, followed by CF_3COOH hydrolysis.¹⁴⁵ The method was used to synthesize (\pm)-flavinantine ($\text{R}^1 = \text{R}^3 = \text{CH}_3$, $\text{R}^4 = \text{H}$) in 63% yield, (\pm)-palladine ($\text{R}^1 = \text{R}^4 = \text{CH}_3$, $\text{R}^3 = \text{H}$) in 50% yield, and amurine ($\text{R}^3, \text{R}^4 = \text{CH}_2$; $\text{R}^1 = \text{CH}_3$) in 80% yield.

A different mode of oxidative coupling is found during the anodic oxidation of 1-(3,4-dimethoxybenzyl)-2-methyl-6,7-dimethoxy-1,4-dihydro-3(2*H*)-

¹³⁹ L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Am. Chem. Soc.* **93**, 5941 (1971).

¹⁴⁰ L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Am. Chem. Soc.* **95**, 2651 (1973).

¹⁴¹ J. Y. Becker, L. L. Miller, and F. R. Stermitz, *J. Electroanal. Chem.* **68**, 181 (1976).

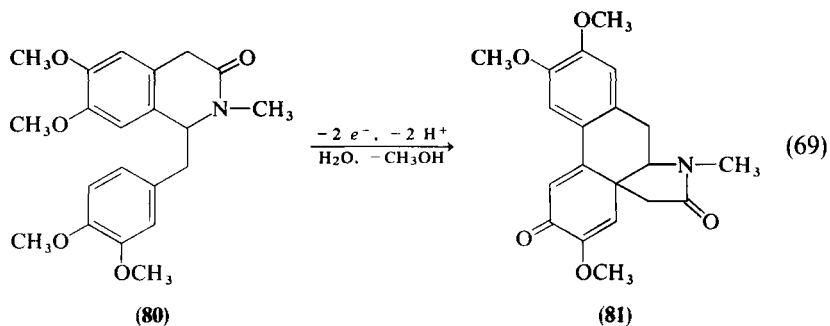
¹⁴² L. L. Miller and R. F. Stewart, *J. Org. Chem.* **43**, 1580 (1978).

¹⁴³ J. B. Kerr, T. C. Jemmy, and L. L. Miller, *J. Am. Chem. Soc.* **101**, 7338 (1979).

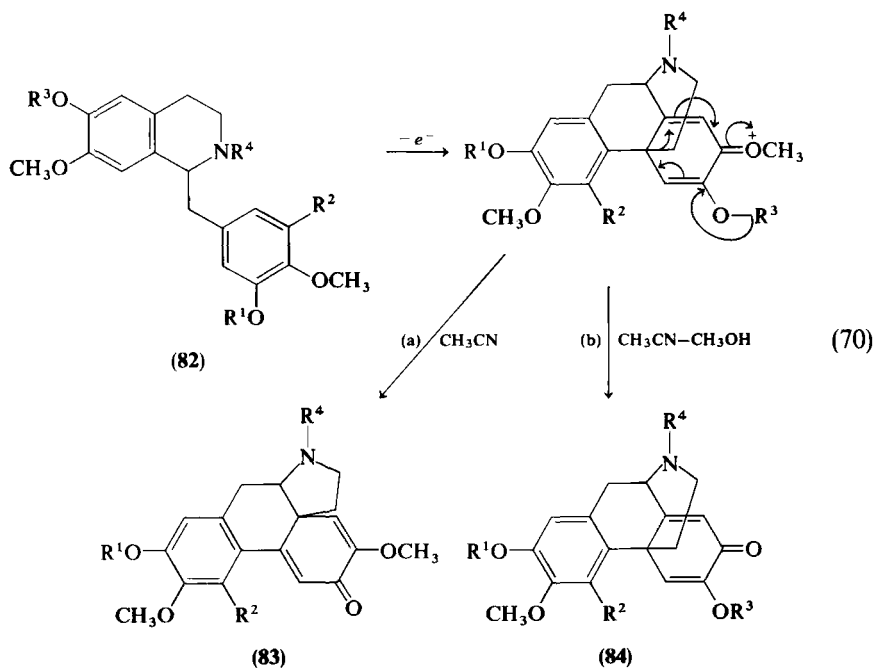
¹⁴⁴ L. Christensen and L. L. Miller, *J. Org. Chem.* **46**, 4876 (1981).

¹⁴⁵ E. Kotani and S. Tobinaga, *Tetrahedron Lett.*, 4759 (1973).

isoquinolone (**80**) in $\text{CH}_2\text{Cl}_2\text{-CF}_3\text{COOH}$ solution to 6,12-dioxo-2,3,7-trimethoxy-11-methyl-6,8*a*,9,10-tetrahydro-9,8*a*-iminoethanophenanthrene (**81**) in 48% yield¹⁴⁶ [Eq. (69)].



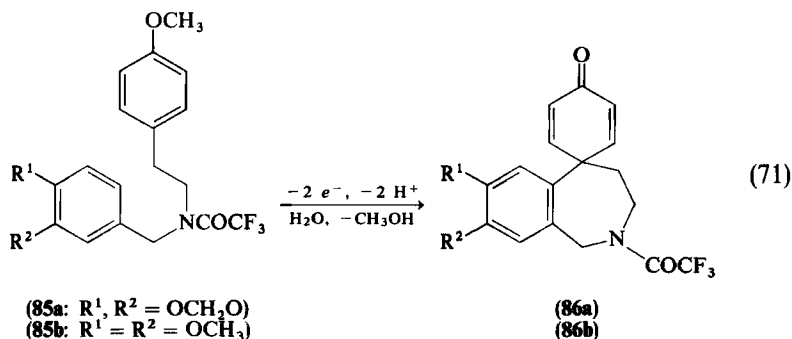
The solvent may influence the course of such coupling reactions. Thus *N*-trifluoroacetyl-1-benzyltetrahydroisoquinolines (**82**) cyclize on anodic oxidation in acetonitrile to neospirodienones (**83**), whereas morphinandienones (**84**) are formed in methanol-acetonitrile [Eq. (70)].¹⁴⁷



¹⁴⁶ I. W. Elliott, Jr., *J. Org. Chem.* **42**, 1090 (1977).

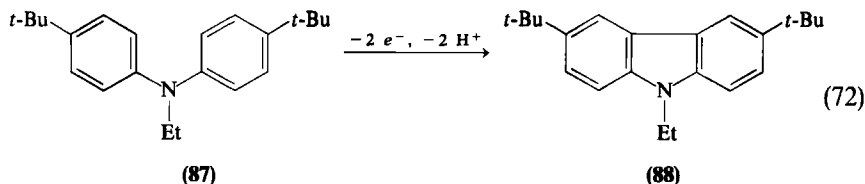
¹⁴⁷ H. Klünenberg, C. Schäfer, and H.-J. Schäfer, *Tetrahedron Lett.* **23**, 4581 (1982).

The results mentioned above^{139,145} prompted the use of a biogenetic-type anodic oxidation of crinine and maritidine. Compound **85a** was oxidized in $\text{CH}_3\text{CN-HBF}_4$ to **86a**. Alkaline hydrolysis of **86a** afforded (\pm) -oxocrinine. Similarly, compound **85b** gave **86b** in 62% yield; **86b** on hydrolysis gave (\pm) -oxomaritidine¹⁴⁸ [Eq. (71)].



A number of related couplings have been reported during the synthesis of the alkaloid (\pm) -cryptopleurine¹⁴⁹ and also intramolecular coupling of diaryl amides to dibenzazepine and dibenzazocine structures.¹⁵⁰ A versatile method for the preparation of tetrahydroquinolines and jololidines has been developed.¹⁵¹ The method involves the anodic oxidation of *N,N*-dimethylaniline in methanol to afford α -methoxylated or α, α' -dimethoxylated compounds and subsequent treatment of products with Lewis acids in the presence of olefins.

The conversion of substituted diphenylamines and triphenylamines to carbazoles at platinum anodes in $\text{CH}_3\text{CN-Et}_4\text{NClO}_4$ takes place if the intermediate cation-radical is fairly stable. Thus the anodic oxidation of *N*-ethylbis(*p*-*tert*-butylphenyl)amine (**87**) gave 3,6-di-*tert*-butyl-*N*-ethylcarbazole (**88**) in 15% yield¹⁵² [Eq. (72)].



¹⁴⁸ E. Kotani, W. Takeuchi, and S. Tobinaga, *J. C. S. Chem. Commun.*, 550 (1973).

¹⁴⁹ E. Kotani, M. Kitazawa, and S. Tobinaga, *Tetrahedron* **30**, 3027 (1974).

¹⁵⁰ M. Sainsbury and J. Wyatt, *J. C. S. Perkin I*, 661 (1976).

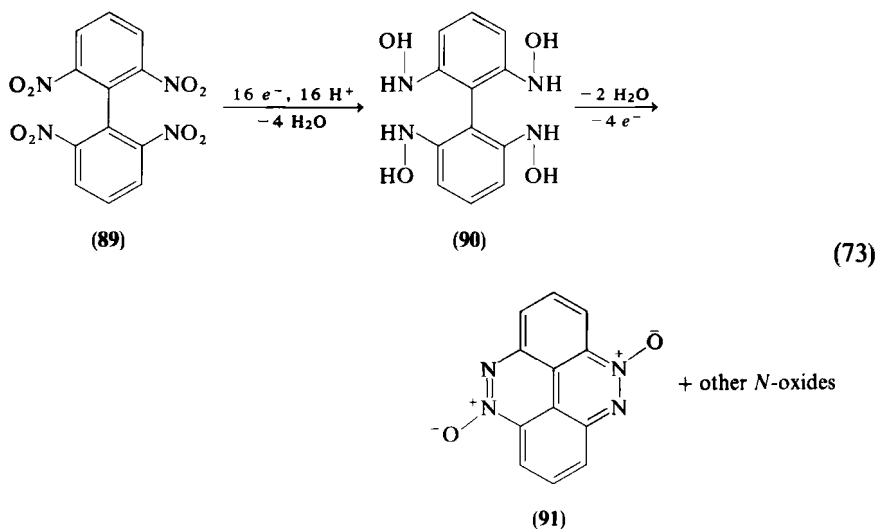
¹⁵¹ T. Shono, Y. Matsumura, K. Inoue, H. Ohmizu, and S. Kashimura, *J. Am. Chem. Soc.* **104**, 5753 (1982).

¹⁵² R. Reynolds, L. L. Line, and R. F. Nelson, *J. Am. Chem. Soc.* **96**, 1087 (1974).

4. Formation of Nitrogen–Nitrogen Bonds

The mechanism of the reductive ring closure by formation of a nitrogen–nitrogen bond is often closely related to the mechanism of the formation of azoxy compounds. This has mostly been formulated as an attack of the nucleophilic hydroxylamino group on the positive center in the nitroso group, followed by loss of water. Inasmuch as the system $\text{ArNO} + 2 e^- + 2 \text{H}^+ \rightleftharpoons \text{ArNHOH}$ generally is electrochemically reversible, it is not unlikely that the reaction is initiated by the transfer of a single electron from the hydroxylamine to the nitroso group, which then forms an anion–radical; a radical–radical coupling then establishes the N–N bond.

Besides some reinvestigations of the formation of benzocinnoline derivatives from 2,2'-dinitrobiphenyl, a similar ring closure by reduction of 2,2',6,6'-tetranitrobiphenyl (**89**) to the hydroxylamine (**90**) followed by oxidation to the mono-, di-, tri-, and tetra-*N*-oxides of 4,5,9,10-tetraazapyrene (**91**) has been reported^{153–155} [Eq. (73)].



Some discussion has arisen concerning the products and mechanism of the formation of dibenzo[*b,f*]-1,4,5-thiadiazepine derivatives from di-(2-nitrophenyl) sulfide (**91**). In one investigation¹⁵⁶ it was concluded that the dibenzothiadiazepine was formed by reaction of a nitroso group with an

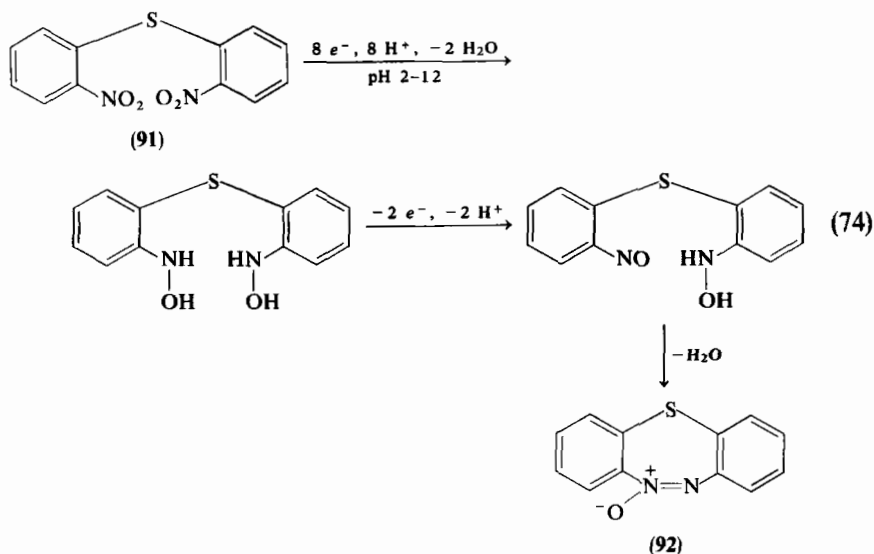
¹⁵³ E. Laviron and T. Lewandowska, *Bull. Soc. Chim. Fr.*, 3177 (1970).

¹⁵⁴ E. Laviron, D. Bernard, and G. Tainturier, *Tetrahedron Lett.*, 3643 (1972).

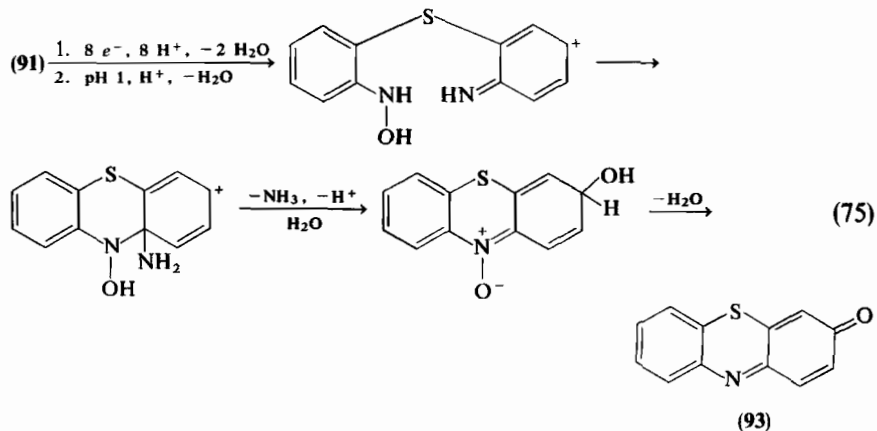
¹⁵⁵ D. Bernard, G. Tainturier, and E. Laviron, *Bull. Soc. Chim. Fr.*, 1645 (1973).

¹⁵⁶ J. Hlavaty, J. Volke, and D. Manousek, *Electrochim. Acta* **23**, 589 (1978).

amino group, whereas another group¹⁵⁷ concluded that the product of the ring closure was the dibenzo[*b,f*]-1,4,5-thiadiazepine-4-*N*-oxide (**92**) formed by reaction between a nitroso and a hydroxylamino group. In view of the remarks made in the beginning of this section, the latter reaction seems the most likely.

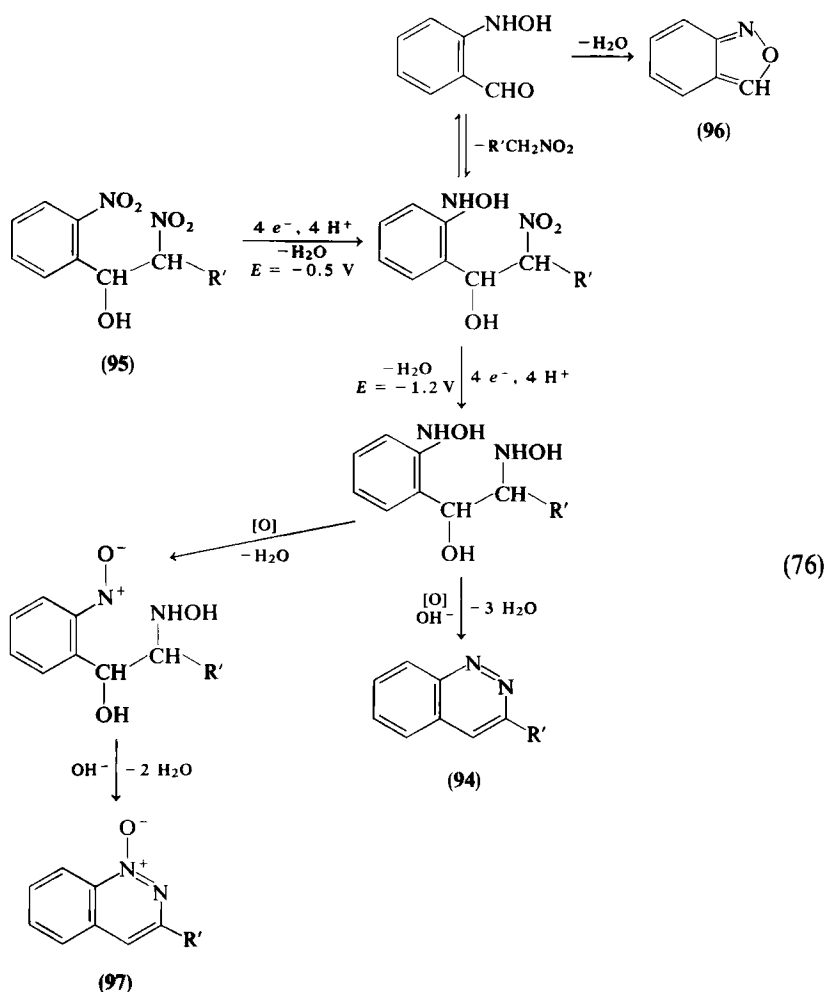


In acidic solution the reaction is different, and after workup (oxidation by air), 3-phenothiazinone (**93**) was isolated. It seems likely that the ring closure begins with a protonation of the hydroxylamino group, followed by loss of water and attack of the other hydroxylamino group on the electrophilic center of the C=N bond [Eq. (75)].



¹⁵⁷ Y. Mugnier and E. Laviron, *Electrochim. Acta* **25**, 1329 (1980).

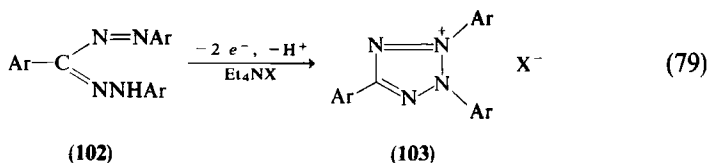
It was previously mentioned¹ that cinnoline and 3-substituted cinnolines (**94**) could be prepared from the condensation products (**95**) between an *o*-nitrobenzaldehyde and a nitroalkane by electrochemical reduction. The reaction has been further studied,¹⁵⁸ and it was noticed that when the reduction was carried out stepwise, anthranils (**96**) were formed, especially at elevated temperatures. The final ring closure was catalyzed by traces of oxygen, whereas too much oxygen produced the cinnoline *N*-oxide (**97**); the ring closure was believed to be a radical chain reaction where the formation of the aromatic cinnoline was part of the driving force [Eq. (76)].



¹⁵⁸ H. Lund and N. H. Nilsson, *Acta Chem. Scand., Ser. B* **B30**, 5 (1976).

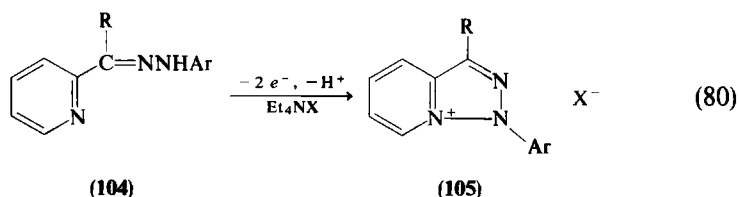
¹⁶¹ R. Hazard and A. Tallec, *Bull. Soc. Chim. Fr.*, 433 (1976).

Anodic oxidation of formazans (102) in $\text{CH}_3\text{CN}-\text{Et}_4\text{NX}$ ($\text{X}=\text{ClO}_4$, *p*-TsO, or BF_4) at a platinum anode produces tetrazolium salts (103) in quantitative yield¹⁶²⁻¹⁶⁴ [Eq. (79)].



Electrochemical oxidation of formazans is a particularly advantageous preparative route to tetrazolium salts, which can be performed by controlled-potential or constant-current electrolysis. Tetrazolium salts with widely differing anions can be prepared by merely using a supporting electrolyte carrying the desired anion. The two-electron oxidative cyclization of formazan to tetrazolium salt may occur through an ECPE(d) mechanism.

A novel way of preparing *s*-triazolo[3,4-*a*]pyridinium salts (105) by anodic oxidation of aryl hydrazones (104) of 2-acetylpyridine, 2-benzoylpyridine, and 2-formylpyridine in $\text{CH}_3\text{CN}-\text{Et}_4\text{NX}$ ($\text{X}=\text{ClO}_4$, *p*-TsO, or BF_4) has been reported¹⁶⁵ [Eq. (80)].



Electrochemical oxidative cyclization is superior to chemical oxidation with lead tetraacetate¹⁶⁶: (i) the products are obtained in high yield (79–91%) and purity, (ii) pyridinium salts with different anions can be prepared by using a supporting electrolyte carrying the desired anion, (iii) the configuration of the substrate does not affect the yield of the product, e.g., both *cis*

¹⁶² H. Lund, "Elektrodereaktioner i Organisk Polarografi og Voltammetri," p. 136. Aarhus Stiftsbogtrykkeri, Aarhus, 1961.

¹⁶³ M. Lačan, I. Tabaković, and Z. Ceković, *Tetrahedron* **30**, 2911 (1974).

¹⁶⁴ I. Tabaković, M. Trkovnik, and Z. Grujić, *J. C. S. Perkin II*, 166 (1979).

¹⁶⁵ M. Batusić, I. Tabaković, and S. Crljenak, *Croat. Chem. Acta* **54**, 397 (1981).

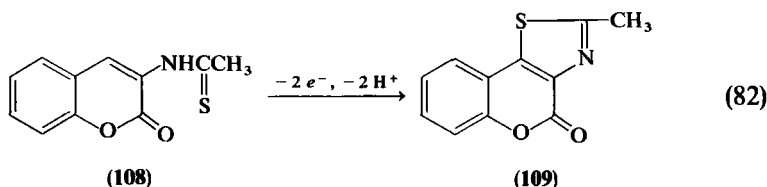
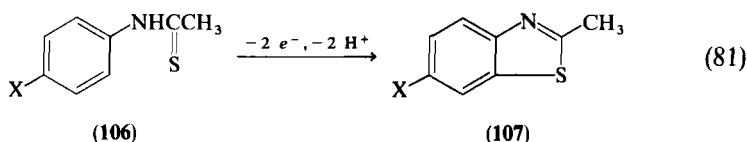
¹⁶⁶ R. Kuhn and W. Münzing, *Chem. Ber.* **85**, 29 (1952).

and trans **104** gave **105** in high yield, (iv) the products are formed by oxidation of the *p*-nitrophenylhydrazone of 2-formylpyridine (**104**; R = H).

A similar anodic cyclization^{167,168} is the oxidation of benzilmonoxime phenylhydrazone to 2,4,5-triphenyl-1,2,3-triazole 1-oxide (83% yield) and of 3-hydroxyiminomethylenamino-6-chloropyridazine to 6-chloro-*s*-triazole-[1,5-*b*]pyridazine 3-oxide (28% yield).¹⁶⁷

5. Formation of Carbon–Sulfur Bonds

The first published example of the anodic cyclization with carbon–sulfur bond formation was the oxidation of thiobenzanilide to 2-phenyl-1,3-benzothiazole.¹²⁰ The oxidation of the thioacetanilides (**106**) and *N*-(3-coumaryl)thioacetamide (**108**) at a platinum electrode in CH₃CN–Et₄NClO₄ gave the expected 1,3-thiazole derivatives **107** and **109** in 60–75% yield¹⁶⁹ [Eqs. (81) and (82)].



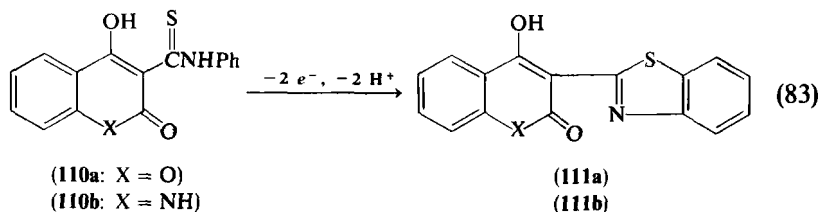
Anodic cyclization of thiocarboxamides to 1,3-thiazoles is in certain cases a superior method compared to the chemical oxidation as usually performed, using an alkaline solution of potassium hexacyanoferrate(III). Thus anodic oxidation of 3-anilinothiocarbonyl-4-hydroxycoumarin (**110a**; X = O) and 3-anilinothiocarbonyl-4-hydroxy-2-quinolone (**110b**) yielded the corresponding 1,3-thiazole derivatives **111a** and **111b**, respectively. Chemical oxidation

¹⁶⁷ I. Tabaković, M. Trkovnik, and D. Galijas, *J. Electroanal. Chem.* **86**, 241 (1978).

¹⁶⁸ N. Henning, T. Dassler, and W. Jugelt, *Z. Chem.* **22**, 25 (1982).

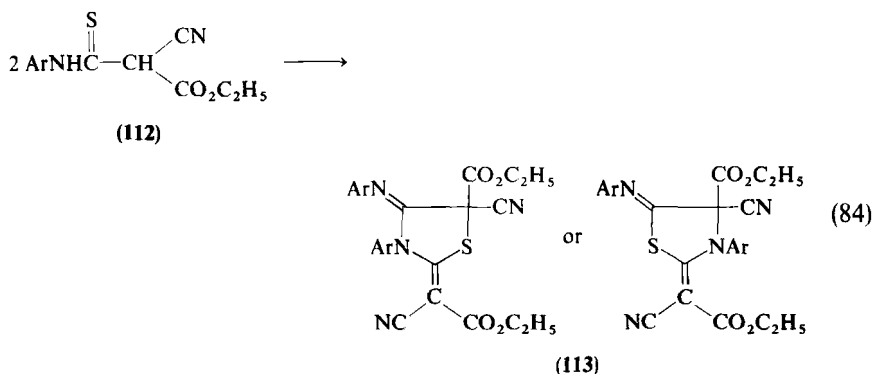
¹⁶⁹ I. Tabaković, M. Trkovnik, M. Batusić, and K. Tabaković, *Synthesis*, 590 (1979).

proceeded in 10–20% yield, whereas the electrochemical yields of **111a** and **111b** were markedly improved to 85 and 90%, respectively¹⁶⁹ [Eq. (83)].



Anodic cyclization of *N*-(2-pyridyl)thiobenzamide to 2-phenyl-1,2,4-thiadiazolo[2,3-*a*]pyridinium perchlorate (80% yield) occurred with N—S and not with C—N bond formation as expected by analogy to the chemical oxidation of structurally similar heterocyclic thiocarboxamides.¹⁶⁹

Anodic oxidation of α -cyano- α -carbethoxy thioacetanilides (**112**) in $\text{CH}_3\text{CN}-\text{Et}_4\text{NClO}_4$, containing pyridine as a base, resulted in formation of dimeric thiazolidine compounds (**113**). A scheme was proposed¹⁷⁰ [Eq. (84)].



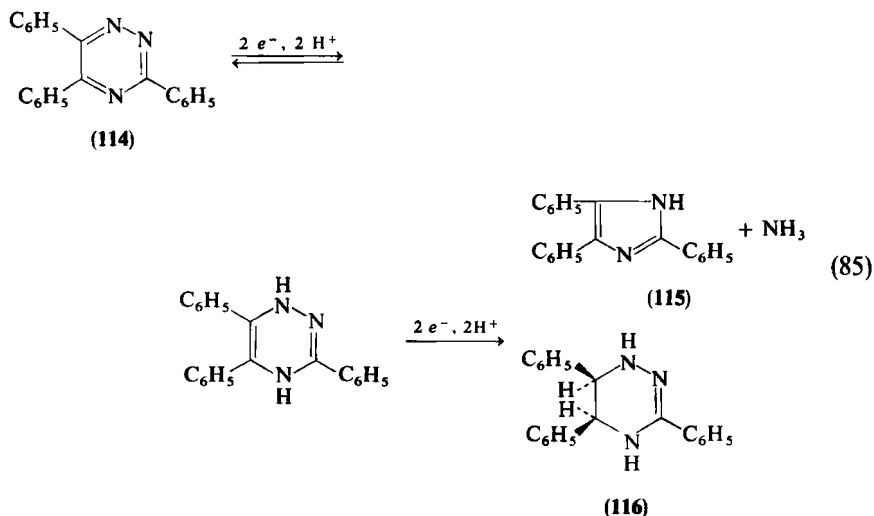
B. RING CONTRACTIONS

Ring contractions may occur during reductions or oxidations. In Part I¹ the ring contractions that were described included reductions of pyridazines

¹⁷⁰ D. Berube, G. Cauquis, G. Pierre, and H. M. Fahmy, *Electrochim. Acta* **27**, 281 (1982).

to pyrroles, cinnolines to indoles, phthalazines to isoindoles, benzo-1,2,4-triazines to benzimidazoles, and benzo-1,2,3-triazinones to indazolones. The mechanism of the latter has been reinvestigated.¹⁷¹ All these reactions involve a cleavage of a bond between two heteroatoms, followed by a nucleophilic attack of the nucleophile formed in the cleavage on an electrophilic center; the reaction is usually terminated by an elimination.

3,5,6-Triphenyl-1,2,4-triazine (**114**) is reduced in aqueous media in two-electron steps; the first reduction produces a mixture of isomeric dihydro derivatives, whereas reduction at the potential of the second step gives a mixture of 2,4,5-triphenylimidazole (**115**) and 1,4,5,6-tetrahydro-3,5,6-triphenyl-1,2,4-triazine¹⁷² (**116**) [Eq. (85)].

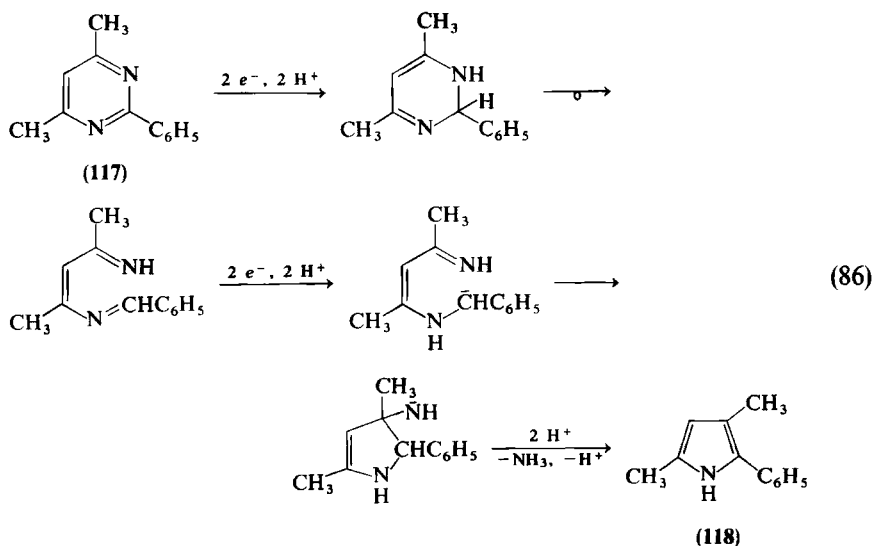


Another type of ring contractions occurs when 2-phenylpyrimidines (**117**) are reduced in an aqueous alcoholic-acetate buffer. Whereas pyrimidines generally are reduced in a one-electron reduction to a dimer,¹ 2-phenylpyrimidines are reduced to 2-phenylpyrroles (**118**). The following scheme has been suggested¹⁷³ [Eq. (86)].

¹⁷¹ H. H. Holst and H. Lund, *Acta Chem. Scand.*, Ser. B **B33**, 233 (1979).

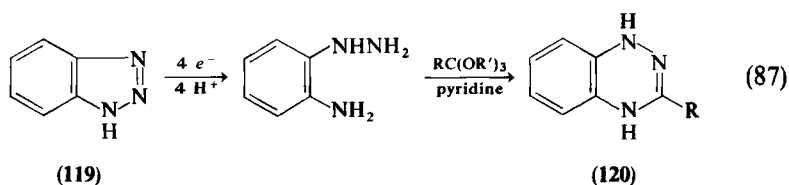
¹⁷² J. Pinson, J. P. M'Packo, N. Vinot, J. Armand, and P. Bassinet, *Can. J. Chem.* **50**, 1581 (1972).

¹⁷³ P. Martigny and H. Lund, *Acta Chem. Scand.*, Ser. B **B33**, 575 (1979).



C. RING EXPANSIONS

A kind of reductive ring expansion is reported in which benzotriazole (**119**) is converted to a dihydrobenzo-1,2,4-triazine (**120**).¹⁷⁴ The reaction involves the known ring opening of benzotriazole to 2-aminophenylhydrazine¹⁷⁵ by reduction in hydrochloric acid, followed by a condensation with a suitable orthoester; the yields are good, and it is probably the most convenient way to prepare derivatives of benzo-1,2,4-triazine [Eq. (87)].



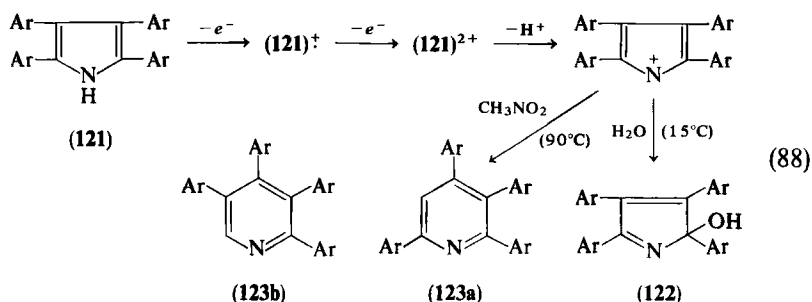
Only a few examples of ring expansions by anodic oxidation have been reported. 2,3,4,5-Tetraphenylpyrrole in nitromethane is oxidized in two one-electron waves, the first being reversible. The same two-electron oxidation

¹⁷⁴ M. Falsig and P. E. Iversen, *Acta Chem. Scand., Ser. B* **B31**, 15 (1977).

¹⁷⁵ H. Lund and S. Kwee, *Acta Chem. Scand.* **22**, 2879 (1968).

products were obtained regardless of whether the reaction was carried out at the first or second wave. Evidence suggests that the radical-cation disproportionates to the starting material and the dication. The dication then reacts with residual water to give a hydroxylated compound that on heating rearranges to a pyrrolone. At higher temperatures the dication reacts with nitromethane, forming nitrite and, reportedly, 2,3,4,6-tetraphenylpyridine,¹⁷⁶ but a 2,3,4,5-tetraphenylpyridine seems more likely.²

The electrochemical oxidation of 2,3,4,5-tetraanisylpyrrole (**121**) in nitromethane at the second wave resulted in the formation of a cation, the reaction of which depended on the reaction temperature [Eq. (88)]. At 15°C a 90% yield of 2-hydroxy-2,3,4,5-tetraanisylpyrrole (**122**) was formed, whereas at 90°C the major product resulted from incorporation of a nitromethane molecule into the ring, giving a tetraanisylpyridine (**123a** or **123b**)¹⁷⁷ [Eq. (88)].



Several other derivatives, e.g., 2,3,4,5-tetra-*p*-tolylpyrrole,¹⁷⁸ tetra(*p*-chlorophenyl)- and tetra(biphenyl)pyrroles^{179,180} showed a similar behavior.

IV. Electrolytic Reactions of Heterocyclic Systems

The electrode reactions of heterocyclic compounds in which a reduction or oxidation of the nucleus takes place are now discussed. Ring systems carrying substituents are included if the substituent is not reduced (or oxidized) and the redox reactions of the ring are not changed in type by the substituent.

¹⁷⁶ M. Libert and C. Caillet, *Bull. Soc. Chim. Fr.*, 1947 (1971).

¹⁷⁷ M. Libert, C. Caillet, and J. Huguet, *Bull. Soc. Chim. Fr.*, 3639 (1972).

¹⁷⁸ M. Libert, C. Caillet, and G. Barbey, *Bull. Soc. Chim. Fr.*, 536 (1973).

¹⁷⁹ M. Libert and C. Caillet, *C. R. Acad. Sci., Ser. C* **276**, 1073 (1973).

¹⁸⁰ M. Libert and C. Caillet, *Bull. Soc. Chim. Fr.*, 800 (1974).

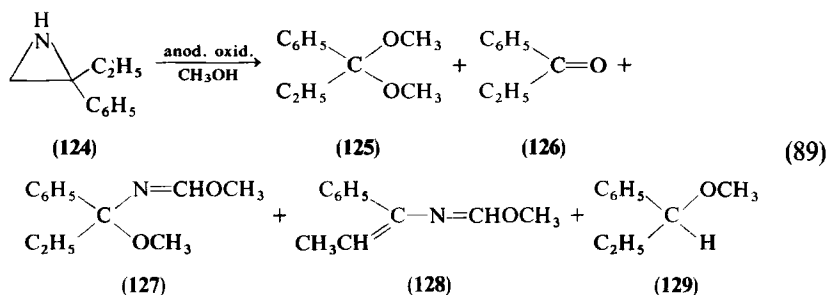
A. COMPOUNDS WITH ONE NITROGEN ATOM

1. Aziridinium Salts

Dialkylaziridinium salts are reducible both in aqueous and aprotic media. In aqueous solution the data are consistent with one two-electron reaction. The products obtained from a preparative electrolysis stem in part from the electrode reaction, but side reactions between primary products and starting material complicate the product mixture.¹⁸¹

Arylaziridinium salts exhibit an unusual behavior in aqueous buffer solution in that the half-wave potentials become more negative on introduction of electron-attracting groups; this is contrary to expectation. The abnormal substituent effect for aziridinium salts can be interpreted as involving development of a partial positive charge at the benzylic carbon before electron transfer.¹⁸²

Oxidation of 2-phenyl-2-ethylaziridine (**124**) in $\text{CH}_3\text{OH}-\text{NaClO}_4$ containing sodium carbonate buffer at constant current gave, after passage of 4 F/mol **125** (50%), **126** (6%), **127** (12%), **128** (1%), and **129** (<1%), respectively [Eq. (89)]. The process is explained by the formation of a highly reactive intermediate azaallyl cation, which loses two electrons and one proton, and then the ring cleaves.¹⁸³



When 1-benzylaziridine (**130**) is oxidized anodically in organic solvents (CH_3OH , CH_3CN , or CH_2Cl_2), using Bu_4NClO_4 as supporting electrolyte, the tetramer (tetraazacyclododecane) (**131**) is obtained in good yield (7–67%) and with very low electrical consumption (0.05–0.37 F/mol) [Eq. (90)]. The tetramerization is also possible by means of an electrogenerated oxidizing reagent.¹⁸⁴ The experimental results exclude the deprotonation of the radical–

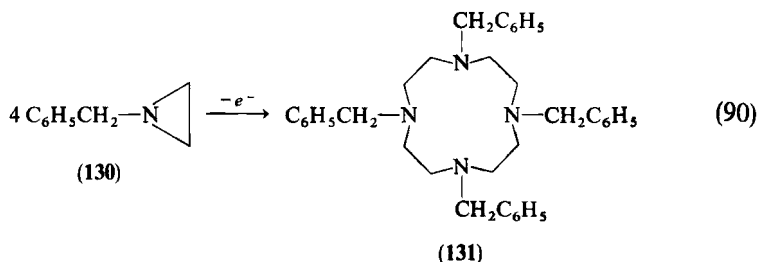
¹⁸¹ D. A. Tyssee and M. M. Baizer, *J. Electrochem. Soc.* **118**, 1420 (1971).

¹⁸² M. B. Kass, A. P. Borsetti, and D. R. Christ, *J. Am. Chem. Soc.* **95**, 959 (1973).

¹⁸³ P. G. Gassman, I. Nishigushi, and H. Yamamoto, *J. Am. Chem. Soc.* **97**, 1600 (1975).

¹⁸⁴ R. Kossai, J. Simonet, and G. Dauphin, *Tetrahedron Lett.*, 3575 (1980).

cation and favor a fast opening of the three-membered ring. A chain mechanism for the formation of **131** is proposed.



2. Pyrrole Derivatives

Anodic oxidation of pyrrole and N-substituted pyrroles results in the formation of polypyrroles in an oxidized state, which can be useful for the preparation of conducting organic polymers.¹⁸⁵⁻¹⁸⁸ Oxidation of 2,5-disubstituted pyrroles produces soluble products and no layer of polymers.¹⁸⁷ One of the proposed applications of such a layer of conducting polymer is the protection of semiconductor electrodes from photocorrosion.¹⁸⁹⁻¹⁹¹

Pentaphenylpyrroles are oxidized anodically to a relatively persistent radical-cation whose spectroscopic characteristics, both optical and ESR, have been described. In general, these radicals have the charge mainly within the heterocyclic nucleus; however, when the para substituent in the phenyl rings is N(CH₃)₂, the radicals have a high charge density at the substituents. Tetraarylpyrroles form radical-cations of variable reactivity, which have been studied by electrochemical methods.^{176-180,192}

In methanolic cyanide, N-substituted pyrroles¹⁹³ are substituted in the 2-position by a cyano group on anodic oxidation. Methoxylation, which is often observed as a side reaction in the anodic oxidation in methanolic cyanide, was suppressed completely. When N-substituted pyrroles carry a methyl group in the 2- and 5-positions, a side-chain cyanation occurs.^{193,194}

¹⁸⁵ A. F. Diaz, K. K. Kanazawa, and G. P. Gardini, *J. C. S. Chem. Commun.*, 635 (1979).

¹⁸⁶ A. F. Diaz, J. I. Castillo, J. A. Logan, and W.-Y. Lee, *J. Electroanal. Chem.* **129**, 115 (1981).

¹⁸⁷ A. F. Diaz, A. Martinez, K. K. Kanazawa, and M. Salmon, *J. Electroanal. Chem.* **130**, 181 (1981).

¹⁸⁸ R. A. Bull, F. R. F. Fan, and A. J. Bard, *J. Electrochem. Soc.* **129**, 1009 (1982).

¹⁸⁹ R. Noufi, A. J. Frank, and A. J. Nozik, *J. Am. Chem. Soc.* **103**, 1849 (1981).

¹⁹⁰ R. Noufi, D. Tench, and L. F. Warren, *J. Electrochem. Soc.* **128**, 2596 (1981).

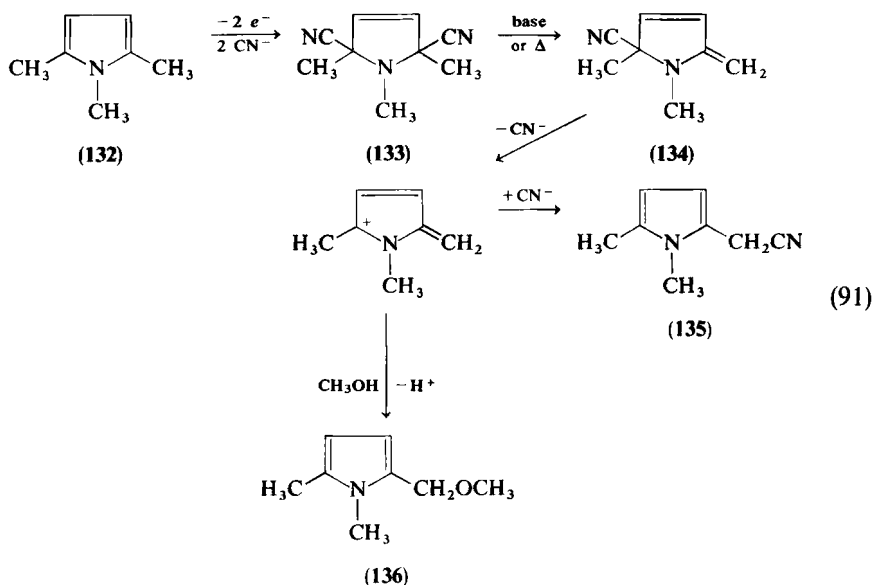
¹⁹¹ R. A. Simon, A. J. Ricco, and M. S. Wrighton, *J. Am. Chem. Soc.* **104**, 2031 (1982).

¹⁹² G. Cauquis and M. Genies, *Bull. Soc. Chim. Fr.*, 3220 (1967).

¹⁹³ K. Yoshida, *J. Am. Chem. Soc.* **99**, 6111 (1977).

¹⁹⁴ K. Yoshida, *J. Am. Chem. Soc.* **101**, 2116 (1979).

The anodically generated radical-cation may be deprotonated in the presence of cyanide to produce an analog of a benzylic radical, which undergoes anodic oxidation to a cation; the cation reacts with cyanide ion to give a side-chain cyanation product.¹⁹⁴ L. Eberson has studied¹⁹⁵ the anodic oxidation of 1,2,5-trimethylpyrrole (132) in the presence of cyanide to give 2,5-dicyano-1,2,5-trimethyl-3-pyrroline (133) as the primary product. The adduct is very sensitive toward base and slowly eliminates HCN with formation of 134, followed by a carbocation rearrangement to 1,5-dimethylpyrrole-2-acetonitrile (135) and the corresponding methoxy derivative (136) [Eq. (91)]. Thus the formation of a side-chain cyanation product in the anodic cyanation of 132 is the result of secondary reactions of the 2,5-dicyano adduct 133.¹⁹⁵



The 2,5-dicyano adduct was formed by anodic oxidation of 1,2,3,5-tetra-phenylpyrrole in $\text{CH}_3\text{CN}-\text{Et}_4\text{NCN}$.¹⁹⁶

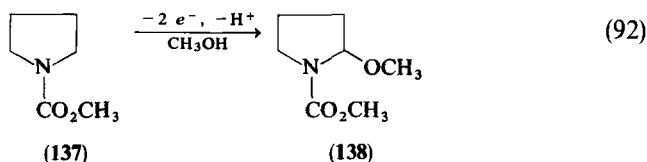
The anodic oxidation of methyl *N,N*-dialkylcarbamate in methanol, containing Et_4NOTs , yielded three types of products: α -methoxylated compounds, enamine-type products, and dealkylated carbamates.¹⁹⁷ Methyl *N*-pyrrolidinylcarbamate (137), for example, gave on constant current oxidation

¹⁹⁵ L. Eberson, *Acta Chem. Scand., Ser. B* **B34**, 747 (1980).

¹⁹⁶ C. Longchamp, C. Caullet, and M. Libert, *Bull. Soc. Chim. Fr.*, 353 (1974).

¹⁹⁷ T. Shono, H. Hamaguchi, and Y. Matsumura, *J. Am. Chem. Soc.* **97**, 4264 (1975).

with a carbon electrode and an undivided cell α -methoxylated **138** in 65% yield [Eq. (92)]. The reaction is general for dialkylamides.^{198,199}



On the basis of oxidation potentials, current-potential relationships, and isotope effects, an electron-transfer mechanism is suggested for the anodic oxidation of methyl N,N-dialkyl substituted carbamates, which can reasonably explain the formation of all three types of products. Also, N-acylazacycloalkanes are converted anodically at a platinum electrode in ROH-Et₄NBF₄ into α -monoalkoxy or α,α' -dialkoxy derivatives depending on the electrolysis conditions employed.¹⁹⁸

The α -methoxylated derivatives are shown to be versatile synthons because of the reactivity of the methoxy group near the nitrogen atom. α -Methoxycarbamates, prepared by anodic oxidation, were used as key intermediates in the synthesis of α -amino acids,²⁰⁰ a new carbon-phosphorus bond-forming reaction,²⁰⁰ and in a new method of acylation of aliphatic amines at the β -position.²⁰¹ The application of this reaction to the synthesis of pyrrolidine, piperidine, and tropane alkaloids is also described.²⁰²

3. Indole Derivatives

The evidence for transient radical-cations from N-substituted indoles has been furnished by the observation of regiocontrolled anodic cyanation of the indole ring.^{193,194} Substitution in the 2-position dominates, although some 3-substitution takes place. When the 1,2,3-positions of indole were blocked, no cyanation occurred, but the products of anodic oxidation have not been isolated.¹⁹⁴

In anodic oxidation of 2,3-diphenylindole (**139**) in CH₃CN-Et₄NClO₄, the initially formed radical-cation dimerizes to a product identified, primarily on the basis of ¹³C-NMR, as a 3-(5-indolyl)indolenine (**140**), which is formed in 90–95% yield²⁰³ [Eq. (93)].

¹⁹⁸ M. Mitzloff, K. Warning, and H. Jensen, *Liebigs Ann. Chem.*, 1713 (1978).

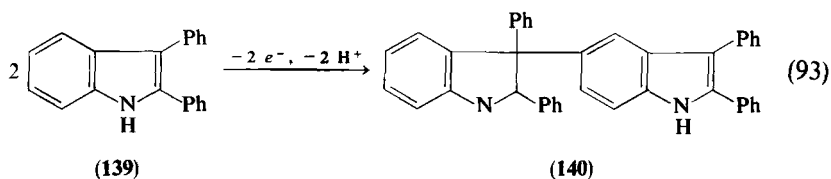
¹⁹⁹ S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Am. Chem. Soc.* **88**, 4657 (1966).

²⁰⁰ T. Shono, Y. Matsumura, and K. Tsubata, *Tetrahedron Lett.* **22**, 2411 (1981); **22**, 3249 (1981).

²⁰¹ T. Shono, Y. Matsumura, K. Tsubata, and Y. Sugihara, *Tetrahedron Lett.* **23**, 1201 (1982).

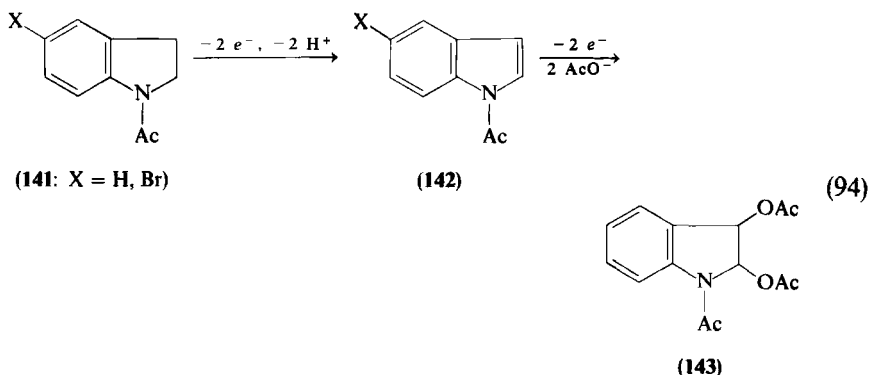
²⁰² T. Shono, Y. Matsumura, and K. Tsubata, *J. Am. Chem. Soc.* **103**, 1172 (1981); T. Shono, *Tetrahedron* **40**, 811 (1984).

²⁰³ G. T. Cheek and R. N. Nelson, *J. Org. Chem.* **43**, 1230 (1978).



The mechanism was first considered²⁰³ to involve radical pairing of the indole radical-cation 139^+ , but later the isolation of a single unsymmetrical dimer was proposed²⁰⁴ as evidence for an ionic mechanism.

Electrochemical acetoxylation of *N*-acetylindolines (141) in AcOH-Et₃N at a platinum electrode afforded the corresponding 2,3-diacetoxyindolines (143).²⁰⁵ The reaction goes in a stepwise manner and the intermediate *N*-acetylindole (142) can be isolated [Eq. (94)].



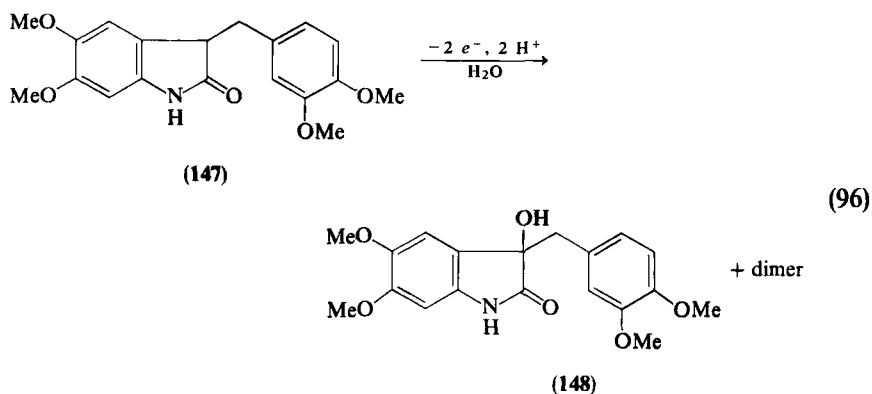
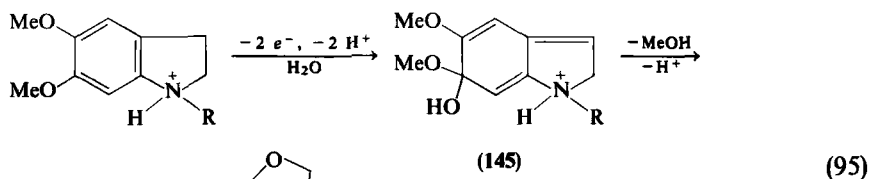
Thermal decomposition of **143** gave *N*-acetyl-3-acetoxyindole, and subsequent hydrolysis with aqueous sodium hydroxide provided indigos in 86–96% yield.

Several compounds containing two oxidizable rings, an indole or indoline, and a dimethoxybenzene, have been oxidized in CH₃CN–NaClO₄.²⁰⁶ The anodic oxidation of the indolinium salt **144** [Eq. (95)] afforded the indole derivative **146** in 15% yield. The oxidation of **144** to **146** is thought to proceed through an intermediate dienol (**145**) because the methoxy group at position 6 on the indoline is lost. The oxidation of the oxindole **147** produces two products, depending on whether the nitrogen is acetylated or free. When the nitrogen is free, 3-hydroxyoxindole (**148**) and a dimeric product were formed in about 28% and 4% yields, respectively [Eq. (96)]. When the nitrogen is acetylated, an intramolecular coupling occurs, similar to that observed in the isoquinoline series.^{139–146}

²⁰⁴ J. M. Bobbitt, C. L. Kulkarni, and J. P. Willis, *Heterocycles* **15**, 495 (1981).

²⁰⁵ S. Torii, T. Yamanaka, and H. Tanaka, *J. Org. Chem.* **43**, 2882 (1978).

²⁰⁶ M. Sainsburg and J. Wyatt, *J. C. S. Perkin I*, 108 (1979).



4. Carbazole Derivatives

Electrochemical and spectroscopic techniques have been used to study the oxidation of carbazole and 71 of its derivatives.^{207,208} Positions 3, 6, and 9 of the carbazole nucleus are the most reactive sites, as expected from Hückel theory. The products isolated are symmetric carbon-carbon (3,3') and nitrogen-nitrogen (9,9') dimers. Substitution of carbazoles in the 3-, 6-, and 9-positions prevents anodic dimerization at these positions; the electrochemical formation of a stable radical-cation is possible.²⁰⁹ The electrochemical oxidation of iminobibenzyl and several related compounds have been investigated in $\text{CH}_3\text{CN}-\text{Bu}_4\text{NClO}_4$ and their electrochemistry was compared with that of related carbazoles.²¹⁰

²⁰⁷ J. F. Ambroze and R. F. Nelson, *J. Electrochem. Soc.* **115**, 1159 (1968).

²⁰⁸ J. F. Ambroze, L. L. Carpenter, and R. F. Nelson, *J. Electrochem. Soc.* **122**, 876 (1975).

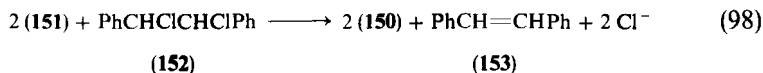
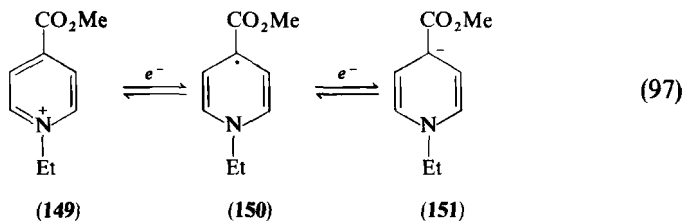
²⁰⁹ W. Lamm, F. Pragst, and W. Jugelt, *J. Prakt. Chem.* **317**, 995 (1975).

²¹⁰ S. N. Frank, A. J. Bard, and A. Ledwith, *J. Electrochem. Soc.* **122**, 898 (1975).

5. Pyridine Derivatives

Pyridine is not polarographically reducible in aqueous solvents¹ but in aprotic media, such as acetonitrile,²¹¹ DMF,²¹² or liquid ammonia,²¹³ it is reduced at rather negative potentials to the anion-radical, which then dimerizes. Some electron-attracting substituents, notably carboxyl derivatives, render the nucleus reducible even in aqueous solvents. Quaternary derivatives are generally reducible. *N*-Alkylpyridinium ions thus give a free radical, which dimerizes rapidly; the radical was trapped by α -phenyl-*N*-tert-butyl nitron.²¹⁴ 1,3-Dimethylpyridinium ion is reduced in buffered aqueous medium to a 4,4'-dimer, which undergoes further chemical reaction, possibly an addition of water to one of the double bonds of the 1,4-dihydropyridine rings.²¹⁵

1-Ethyl-4-methoxycarbonylpyridinium iodide (**149**) is reduced³⁷ in cyclic voltammetry in DMF in two reversible reactions [Eq. (97)] the first leading to a rather stable radical (**150**) and the second to a carbanion (**151**). It was shown (Fig. 8) that **151** was able to transfer an electron to 1,2-dichloro-1,2-diphenylethane (**152**). In Fig. 8, trace *a* shows the irreversible reduction of (**152**) to stilbene (**153**), followed by the reversible reduction of **153**; trace *b* illustrates the reversible reduction of (**149**) to (**150**) and of **150** to **151**. Trace *c* is a CV curve of a mixture of **149** and **152**; the first reduction of **149** is unaffected, whereas the second is increased in height; the irreversible reduction of **152** is not seen, whereas the reversible reduction of **153** is found. The increase in the second peak is caused by a homogeneous electron transfer from **151** to **152**; **150** is then formed at the electrode and reduced again, so the current increases.



²¹¹ J. E. O'Reilly and P. J. Elving, *J. Am. Chem. Soc.* **94**, 7941 (1972).

²¹² B. J. Tabner and I. R. Yandle, *J. Chem. Soc. A*, 381 (1968).

²¹³ O. R. Brown, R. J. Butterfield, and J. P. Millington, *Electrochim. Acta* **27**, 1655 (1982).

²¹⁴ J. G. Gaudiello, D. Larkin, J. D. Rawn, J. J. Sosnowski, E. E. Bancroft, and H. N. Blount, *J. Electroanal. Chem.* **131**, 203 (1982).

²¹⁵ M. G. Bonicelli, M. E. Cardinali, and I. Carelli, *J. Electroanal. Chem.* **131**, 345 (1982).

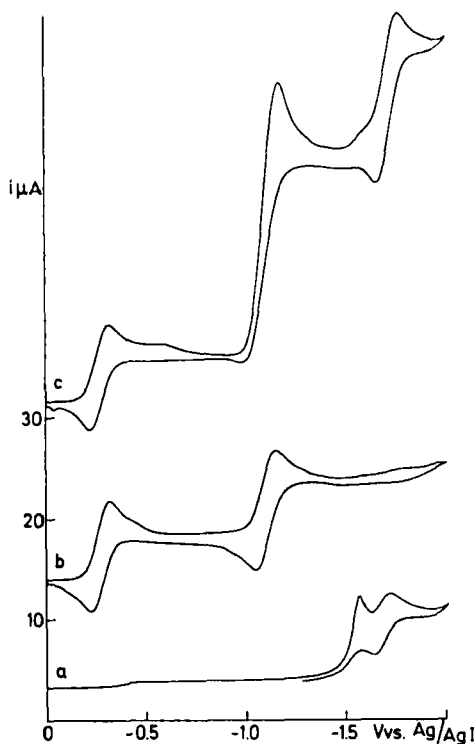
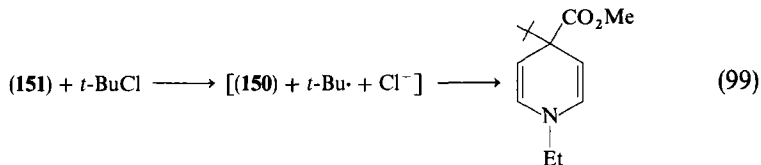


FIG. 8. Cyclic voltammograms in DMF of (a) 1,2-diphenyl-1,2-dichloroethane (**152**), (b) 1-methyl-4-methoxycarbonylpyridinium iodide (**149**), (c) **149** + **152**. (Reprinted from Ref. 37 with permission from *Acta Chemica Scandinavica*.)

When **151** is caused to react with *tert*-butyl chloride, a coupling occurs in high yield [Eq. (99)]; the substitution seems neither to be an S_N1 nor an S_N2 reaction but was suggested to occur via an initial electron transfer from **151** to *t*-BuCl, followed by coupling of the two radicals [Eq. (99)].³⁷ Anion **151** also reacts with carbon dioxide, forming a spiro derivative of malonic acid.



The 1-methyl-2-, 3-, and 4-methoxycarbonylpyridinium ions have been investigated by pulse polarography and reverse pulse polarography. The 4-isomer was found to give a radical stable both in acetonitrile and methanol,

whereas the radical of the 3-isomer dimerized fast and irreversibly, and the 2-isomer dimerized reversibly.²¹⁶

1-Benzyl-3-carbamoylpyridinium chloride (**154**) and analogous compounds have previously been investigated¹ as a NAD^+ model; newer investigations have resulted in structure determination of the dimeric products^{217–219}. By reducing **154** in a benzene–water suspension, a blocking of the electrode surface by the adsorbed dimer was avoided.^{217,218} The products from electrolysis in buffer at pH 8–10 at a potential corresponding to the first polarographic wave were diastereomeric 4,4'-linked dimers. At more negative potentials 1,6- and 1,4-dihydropyridine derivatives were obtained.

The reduction of NAD^+ at a mercury electrode at -1.1 V versus SCE gives a 90% yield of dimers²²⁰; three stereoisomers of 4,4'-dimers were found to account for 90% of the dimer mixture, and three 4,6'-dimers were responsible for the remaining 10%. The dimers were separated, using reverse-phase HPLC and gel filtration on Sephadex G-15; no 6,6'-dimers were detected. Reduction at -1.8 V resulted in 50% 1,4-NADH, 30% 1,6-NADH, and 20% dimers. In other investigations²²¹ the three stereoisomeric 4,4'-dimers have also been obtained as the main products.

1,2,6-Trimethyl-3,5-diethoxycarbonylpyridinium cation is reduced in aqueous acetic acid to a mixture of isomeric dimers. The less stable of these isomers, the 2,4'-dimer, undergoes thermally a rearrangement to the more stable 4,4'-dimer. The mechanism probably involves a dissociation of the 2,4'-dimer to pyridyl radicals, which dimerize to the more stable 4,4'-isomer.²²²

The reduction of bipyridyls was discussed in Part I (see also Refs. 223–226). Paraquat dimer molecules (**155**) held together by a chain of methylene groups are reduced through the cation–radical and further to a diradical; the splitting of the waves depends on the length of the methylene bridge.²²⁷ They have been considered as “two-electron mediators” in indirect electrode

²¹⁶ E. Kashti-Kaplan, J. Hermolin, and E. Kirowa-Eisner, *J. Electrochem. Soc.* **128**, 802 (1981).

²¹⁷ F. M. Moracci, F. Liberatore, V. Carelli, A. Arnone, I. Carelli, and M. E. Cardinali, *J. Org. Chem.* **43**, 3420 (1978).

²¹⁸ I. Carelli, M. E. Cardinali, and F. M. Moracci, *J. Electroanal. Chem.* **107**, 391 (1980).

²¹⁹ Y. Ohnishi and M. Kitami, *Bull. Chem. Soc. Jpn.* **52**, 2674 (1979).

²²⁰ H. Jaegfeldt, *Bioelectrochem. Bioenerg.* **8**, 355 (1981) [*J. Electroanal. Chem.* **128** (1981)].

²²¹ V. Carelli, F. Liberatore, A. Casini, R. Mondelli, A. Arnone, I. Carelli, G. Rotilio, and I. Mavelli, *Bioorg. Chem.* **9**, 342 (1980) [*CA* **94**, 98618 (1981)].

²²² F. T. McNamara, J. W. Niefert, J. F. Ambrose, and E. S. Huyser, *J. Org. Chem.* **42**, 988 (1977).

²²³ H. Erhard and W. Jaenicke, *J. Electroanal. Chem.* **65**, 675 (1975).

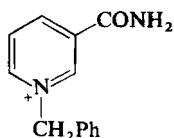
²²⁴ H. Erhard and W. Jaenicke, *J. Electroanal. Chem.* **81**, 79, 89 (1977).

²²⁵ L. Rouiller and E. Laviron, *Electrochim. Acta* **22**, 669 (1977).

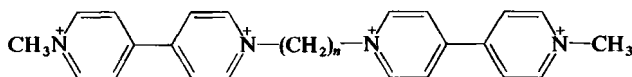
²²⁶ O. R. Brown and R. J. Butterfield, *Electrochim. Acta* **27**, 321 (1982).

²²⁷ A. Deronzier, B. Galland, and M. Vieira, *Nouv. J. Chim.* **6**, 97 (1982).

reactions.²²⁷ Similar results are obtained from isonicotinic esters connected by a methylene chain through the two nitrogen atoms.²²⁸



(154)



(155)

The anodic oxidation of various dihydropyridine derivatives to the corresponding pyridinium or pyridine derivatives has been the subject of several investigations both in protic and aprotic solvents.^{229–237} The great interest in this process is because of the biological importance of the pyridinium–dihydropyridine redox system.

It has been shown²³³ that 1,4-dihydropyridines having no alkyl group in position 4 are oxidized to the corresponding pyridine in a two-electron process, using $\text{CH}_3\text{CN}-\text{H}_2\text{O}(1:1)-\text{LiClO}_4$. When position 4 is occupied by two alkyl groups, the electrode process is stopped after the loss of the first electron, and the resulting intermediate undergoes chemical follow-up reactions.

The substituted 1,4-dihydropyridines **156** in dry acetonitrile, containing Bu_4NClO_4 , are oxidized in a one-electron step leading presumably to a radical-cation (**157**).²³⁵ The final product obtained in dry acetonitrile is a substituted pyridine (**158**) or pyridinium derivative (**159**), a two-electron product. This indicates a disproportionation of the initially formed radical-cation. By adding water to act as a base, the wave doubled in height indicating a deprotonation of the radical cation **157** to a radical that is oxidizable

²²⁸ J. Hermolin, S. Kashti-Kaplan, and E. Kirowa-Eisner, *J. Electroanal. Chem.* **123**, 307 (1981).

²²⁹ J. P. Stradins, G. J. Duburs, J. I. Beilis, J. P. Uldrikjīs, and A. F. Korotkova, *Khim. Geterotsikl. Soedin.*, **84** (1972) [*CA* **76**, 139832 (1972)].

²³⁰ J. P. Stradins, J. I. Beilis, G. J. Duburs, and T. L. Slonskaya, *Lat. PSR Zinat. Akad. Vestis, Kim. Ser.*, 372 (1972).

²³¹ W. J. Blaedel and R. G. Haas, *Anal. Chem.* **42**, 918 (1970).

²³² J. P. Stradins, J. I. Beilis, J. P. Uldrikjīs, G. J. Duburs, A. E. Sausins, and B. S. Cekavicius, *Khim. Geterotsikl. Soedin.*, 1525 (1975) [*CA* **84**, 81644 (1976)].

²³³ V. Skala, J. Volke, V. Ohánka, and J. Kuthan, *Collect. Czech. Chem. Commun* **42**, 292 (1977).

²³⁴ J. Klima, A. Kurfürst, J. Kuthan, and J. Volke, *Tetrahedron Lett.*, 27 (1977).

²³⁵ J. V. Ogle, J. P. Stradins, G. J. Duburs, V. K. Lusiš, and V. F. Kadis, *Khim. Geterotsikl. Soedin.*, 1263 (1980) [*CA* **94**, 111492 (1981)].

²³⁶ F. Pragst, B. Kaltöfen, J. Volke, and J. Kuthan, *J. Electroanal. Chem.* **119**, 301 (1981).

²³⁷ J. Ludvik, J. Klima, J. Volke, A. Kurfürst, and J. Kuthan, *J. Electroanal. Chem.* **138**, 131 (1982).

The importance of 1,4-dihydropyridine nucleotides in biological systems prompted the increasing interest in their electrochemical oxidation.²³⁸⁻²⁴³ The mechanistic aspects of the electrochemical oxidation of NADH involving removal of two electrons and one proton to form NAD^+ has been examined in aqueous and DMSO media at a glassy carbon electrode.²⁴² The reaction occurs according to an ECE mechanism:



According to the ECE mechanism proposed, the first E step would be an irreversible, heterogeneous electron transfer yielding a radical-cation, $\text{NADH}^{\cdot+}$. The large activation energy (overpotential) may be required because NADH must undergo a reorganization of the solvent shell before it can lose an electron. The C step would be a first-order deprotonation reaction leading to the neutral radical, NAD^{\cdot} . The second E step would be a fast heterogeneous electron transfer or solution electron transfer through disproportionation involving the radical-cation $\text{NADH}^{\cdot+}$ and neutral radical NAD^{\cdot} .

The electrochemically oxidized forms of certain tetrahydropteridines,¹⁸ *o*-hydroquinones,²⁴⁴ and aromatic diamines²⁴⁵ are very active NADH oxidants.

6. Quinoline Derivatives

Quinoline has been reductively alkylated in liquid ammonia with primary alkyl bromides^{246,247} and in DMF with tertiary alkyl halides.⁴⁰ In NH_3 approximately equal amounts of 1,4-dialkyl-1,4-dihydroquinoline (**160**) and

²³⁸ R. D. Braun, K. S. V. Santhanam, and P. J. Elving, *J. Am. Chem. Soc.* **97**, 2591 (1975), and references therein.

²³⁹ P. Leduc and D. Thevenot, *J. Electroanal. Chem.* **47**, 543 (1973).

²⁴⁰ P. Leduc and D. Thevenot, *Bioelectrochem. Bioenerg.* **1**, 96 (1974).

²⁴¹ W. J. Bleadel and R. A. Jenkins, *Anal. Chem.* **47**, 1337 (1975).

²⁴² J. Moriroux and P. J. Elving, *J. Am. Chem. Soc.* **102**, 6533 (1980).

²⁴³ I. Carelli, R. Rosati, and A. Casini, *Electrochim. Acta* **26**, 1695 (1981).

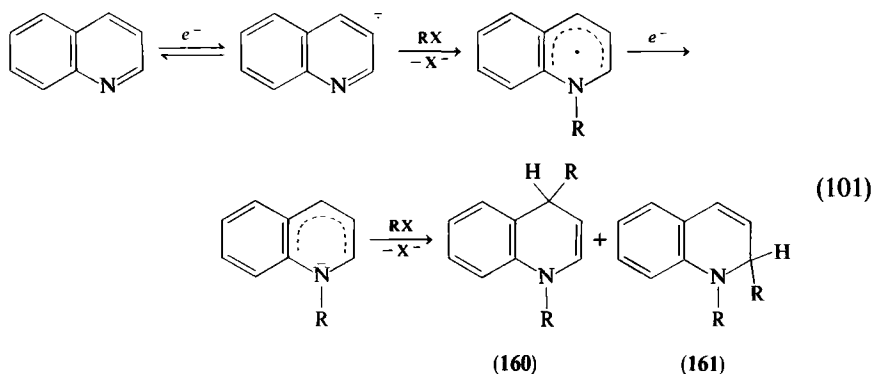
²⁴⁴ D. C. S. Tse and T. Kuwana, *Anal. Chem.* **50**, 1315 (1978).

²⁴⁵ A. Kitani and L. L. Miller, *J. Am. Chem. Soc.* **103**, 3595 (1981).

²⁴⁶ W. H. Smith and A. J. Bard, *J. Am. Chem. Soc.* **97**, 6491 (1975).

²⁴⁷ O. R. Brown and R. J. Butterfield, *Electrochim. Acta* **27**, 1663 (1982).

1,2-dialkyl-1,2-dihydroquinoline (**161**) were formed. The reaction is suggested²⁴⁶ to proceed through an ECEC reaction with *N*-alkylation of the initially formed anion-radical [Eq. (101)].

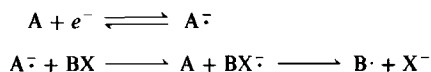


The reductive alkylation with tertiary halides⁴⁰ gives no *N*-alkylation and another product distribution, as discussed below for the alkylation of isoquinoline.

3-Cyanoquinoline is reduced polarographically in ethanol in two one-electron waves; the product from the first reduction is the 4,4'-dimer; reduction at the plateau of the second wave produced 3-cyano-1,4-dihydroquinoline.²⁴⁸

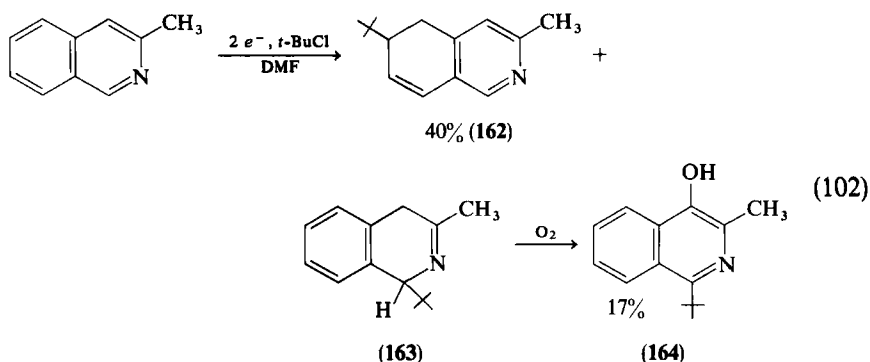
7. Isoquinoline and Acridine Derivatives

Isoquinoline has been alkylated with tertiary halides such as *tert*-butyl⁴⁰ or adamantyl halides.⁴¹ Isoquinoline is reduced more easily than the halides and the mechanism is believed to involve alkyl radicals formed by homogeneous electron transfer from the heteroaromatic anion-radical A^\cdot .

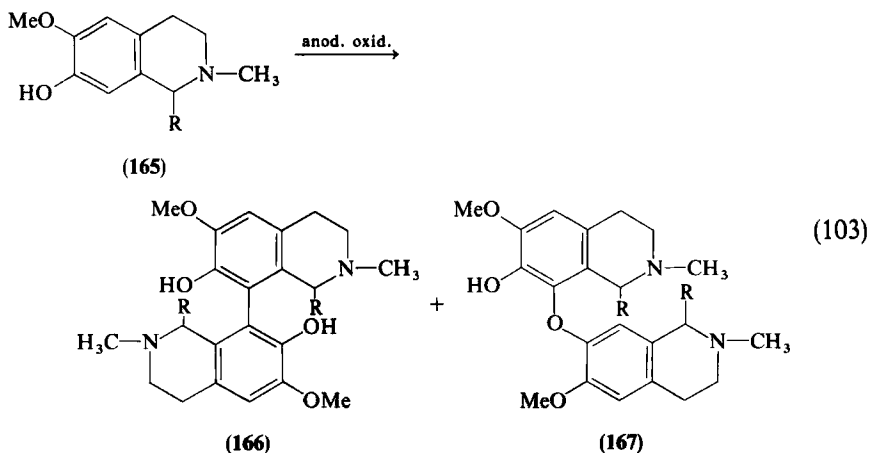


The radical may attack either the anion-radical or isoquinoline; in the latter case, a second electron is transferred from an A^\cdot . The reductive *tert*-butylation of 3-methylisoquinoline gives mainly **162** and **163** together with small amounts of 4-, 5-, or 8-substituted dihydroisoquinolines. Imine **163** was oxidized to **164** during workup⁴⁰ [Eq. (102)].

²⁴⁸ D. N. Schluter, T. Biegler, E. V. Brown, and H. H. Bauer, *Electrochim. Acta* **21**, 753 (1976).



Corypalline (165: R = H)²⁴⁹ could be oxidatively dimerized electrochemically in overall yields ranging from 44 to 85% depending on experimental conditions. Two types of dimers are obtained, the amount of carbon-carbon dimer 166 decreasing when R was varied from H through methyl to ethyl, and the product distribution shifted toward the carbon-oxygen-carbon dimer 167, presumably because of steric hindrance²⁵⁰ [Eq. (103)].



When the sodium salt of 1-methylcorypalline (165: R = CH₃) was oxidized in acetonitrile, a good yield of carbon-carbon dimer (69%) was obtained, in which only one of the enantiomeric pairs was obtained.²⁵¹ The results were explained by proposing a surface mechanism in which the isoquinoline rings are adsorbed in a planar fashion. If the reacting molecules are adsorbed on the surface with methyl groups projecting upward, only those

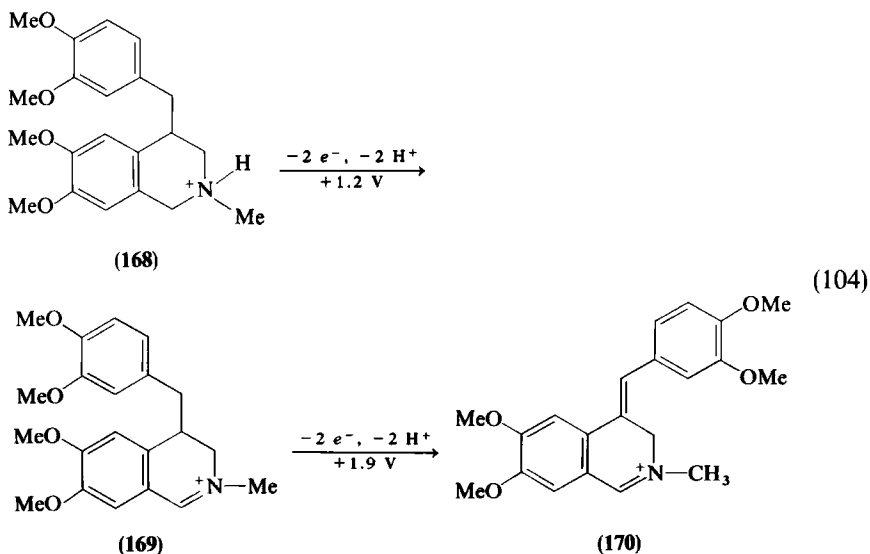
²⁴⁹ G. F. Kirkbright, J. T. Stock, R. D. Pugliese, and J. M. Bobbitt, *J. Electrochem. Soc.* **116**, 219 (1969).

²⁵⁰ J. M. Bobbitt, K. H. Weisgraber, A. S. Steinfeld, and S. G. Weiss, *J. Org. Chem.* **35**, 2884 (1970).

²⁵¹ J. M. Bobbitt, I. Noguchi, H. Yagi, and K. H. Weisgraber, *J. Am. Chem. Soc.* **93**, 3551 (1971).

having identical configurations can come close enough to couple.²⁵² A series of derivatives of 1,2,3,4-tetrahydroisoquinoline has been oxidized electrochemically, and some variables, such as the nature of the anode, cell, solvent, pH, and reaction time, were considered.²⁵³ Attempts to oxidize reticuline and its nor derivative have yielded no isolable products and the starting material was destroyed either by extensive overoxidation or by fragmentation processes.²⁵⁴ Anodic oxidation of *N*-ethoxycarbonyl or *N*-benzyloxy-carbonyl derivatives of norreticuline gave the corresponding dienones as products of intramolecular couplings.²⁵⁵

Anodic oxidation of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**168**) in trifluoroacetic acid–dichloromethane– Bu_4NBF_4 , using controlled-potential electrolysis (+1.2 V versus SCE) affords the corresponding 3,4-dihydroisoquinolinium salt (**169**), and the 4-(3,4-dimethoxybenzylidene)-6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium salt (**170**) was formed at higher anodic potential (+1.9 V versus SCE) at a carbon-felt anode²⁵⁶ [Eq. (104)].



Anodic oxidation of 9,9-substituted 9,10-dihydroacridines in CH_3CN – Bu_4NClO_4 at a Pt electrode gives a cation–radical that dimerizes to a 2,2'-biacridine system; such a dimer is further oxidizable to a quinonoid

²⁵² J. M. Bobbitt, I. Noguchi, H. Yagi, and K. H. Weisgraber, *J. Org. Chem.* **41**, 845 (1976).

²⁵³ J. M. Bobbitt, H. Yagi, S. Shibuya, and J. T. Stock, *J. Org. Chem.* **36**, 3006 (1971).

²⁵⁴ J. M. Bobbitt and R. C. Hallcher, *J. C. S. Chem. Commun.*, 543 (1971).

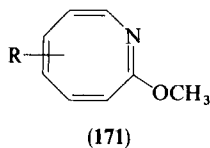
²⁵⁵ J. M. Bobbitt, I. Noguchi, R. S. Ware, K. Ng Chiong, and S. J. Huang, *J. Org. Chem.* **40**, 2924 (1975).

²⁵⁶ M. P. Carmody, M. Sainsbury, and R. F. Newton, *J. C. S. Perkin I*, 2013 (1980).

system.²⁵⁷ Acridine is oxidized at controlled potential at a platinum anode in $\text{CH}_3\text{CN}-\text{NaClO}_4$ to a radical cation that dimerizes, presumably through N—C bond formation, to a cation; such a cation may be oxidized by loss of one electron and one proton to a dimeric radical-cation that is in equilibrium with a tetrameric (on the basis of acridine) dication.²⁵⁸

8. Azocines

Substituted 2-methoxyazocines (**171**) have been studied electrochemically primarily because they are analogs of cyclooctatetraene^{259,260}; the transfer of the first electron from the electrode to **171** is slow, whereas that of the second is fast. The dianion thus formed may exchange an electron with **171** or become protonated.



B. COMPOUNDS WITH ONE NITROGEN AND ONE OXYGEN ATOM

The reduction of oxaziridines, anthranils, and benzoxazines was discussed in Part I.

Oxazoles and Isoxazoles

2,5-Diphenyloxazole^{261–265} has been investigated polarographically in DMF; it is reduced in two one-electron steps, the first reduction giving a

²⁵⁷ E. Sturm, H. Kiese, and E. Daltrozzo, *Chem. Ber.* **111**, 227 (1978).

²⁵⁸ K. Yasukouchi, I. Taniguchi, H. Yamaguchi, and K. Arakawa, *J. Electroanal. Chem.* **121**, 231 (1981).

²⁵⁹ L. B. Anderson, J. F. Hansen, T. Kakihana, and L. A. Paquette, *J. Am. Chem. Soc.* **93**, 161 (1971).

²⁶⁰ B. Svensmark Jensen, T. Petterson, A. Ronlan, and V. D. Parker, *Acta Chem. Scand., Ser. B* **B30**, 773 (1976).

²⁶¹ W. N. Grieg and J. W. Rogers, *J. Electrochem. Soc.* **117**, 1141 (1970).

²⁶² S. L. Smith, L. D. Cook, and J. W. Rogers, *J. Electrochem. Soc.* **119**, 1332 (1972).

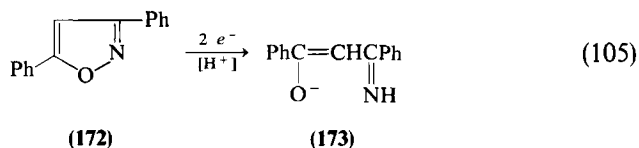
²⁶³ N. P. Shimanskaya, L. A. Kotok, T. F. Alekhina, and V. D. Bezuglyi, *Zh. Obshch. Khim.* **43**, 1445 (1973) [*CA* **80**, 22104 (1974)].

²⁶⁴ N. P. Shimanskaya, L. A. Kotok, B. M. Krosovitskii, L. D. Shcherbak, and T. Alekhina, *Zh. Obshch. Khim.* **46**, 2107 (1976) [*CA* **85**, 200076 (1976)].

²⁶⁵ I. G. Markova, M. K. Polievtov, and S. D. Sokolov, *Zh. Obshch. Khim.* **46**, 398 (1976) [*CA* **84**, 120832 (1976)].

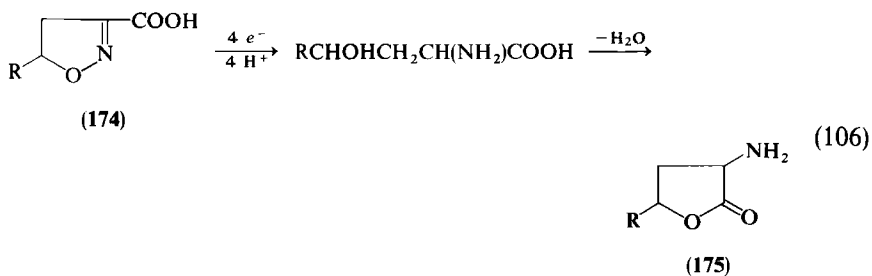
reasonably stable anion-radical, the second a dihydrooxazole. In aqueous acidic solution a six-electron product with ring opening is found (Part I).

In DMF, 3,5-diphenylisoxazole (172) is reduced to the monimine of dibenzoylmethane (173)²⁶⁶ [Eq. (105)]. If a strong proton donor is present, then a further reduction of the imino group to a β -amino ketone, and possibly also of the ketone group, takes place. If no protons are available, then the electro-generated base cleaves the primary product to benzoic acid and acetophenone. *tert*-Butyl chloride is suitable for the formation of 173 because it is not acidic and a buildup of a high concentration of base is prevented because the base eliminates hydrogen chloride from *t*-BuCl with the formation of an alkene. *N*-Alkylisoxazolium compounds may be cleaved similarly in non-aqueous or slightly alkaline solution.²⁶⁶



The suggestion²⁶⁷ that isocarboxazid and 5-methyl-3-carboxyisoxazole are reduced in a four-electron reduction to a tetrahydroisoxazole seems unlikely.

Isoxazolines as cyclic oximes are reduced with initial cleavage of the N—O bond followed by reduction of the C=N bond. 3-Carboxyisoxazolines (174) are thus generally reduced to γ -hydroxy- α -amino acids, which may lactonize (175)²⁶⁸ [Eq. (106)].



The reduction of 2,3-benzoxazin-1-one with ring contraction to a phthalimidine (Part I) has been used as a model for asymmetric induction by an alkaloid; a low concentration (1.4×10^{-4} M) of strychnine induces some chirality during reduction in an acetate buffer (optical yield about 5%).²⁶⁹

²⁶⁶ H. Lund, to be published.

²⁶⁷ Z. I. El-Darawy, H. K. El-Makkawi, and T. M. H. Saber, *Pharmazie* **30**, 94 (1975).

²⁶⁸ H. Lund, unpublished observation.

²⁶⁹ M. Jubault, A. Lebouc, and A. Tallec, *Electrochim. Acta* **27**, 1339 (1982).

C. COMPOUNDS WITH ONE NITROGEN AND ONE SULFUR ATOM

1. Thiazole and Thiazinium Derivatives

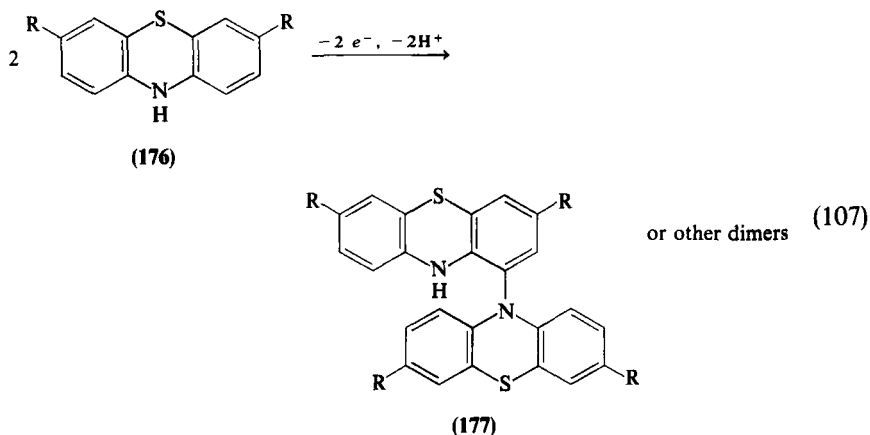
Benzothiazolium salts in aqueous solution with tetraethylammonium perchlorate as supporting electrolyte are reduced in two one-electron steps.²⁷⁰ The first produces a radical that dimerizes with a radical-substrate reaction as the rate-determining step. The product is dimerized in the 2-position. Reduction at the potential of the second step produces the 2,3-dihydrobenzothiazole.

The reduction of some thiazole and isothiazole derivatives was discussed in Part I.

Reduction of 1,3-thiazinium salts in acetonitrile yields 6,6'-di-1,3-thiazinyls formed by dimerization of a short-lived radical; oxidation at a platinum anode regenerates the thiazinium salt, whereas oxidation with chloranil yields 6,6'-di-1,3-thiazinylidenes.²⁷¹

2. Phenothiazine Derivatives

Various phenothiazines (176) have been oxidized in $\text{CH}_3\text{CN}-\text{Et}_4\text{NClO}_4$ to a stable radical-cation ($\text{R} = \text{OCH}_3$). The free radical resulting from deprotonation of the radical-cation gives in those cases where $\text{R} = \text{H}$, SCN , or $t\text{-Bu}$ a C—N bond dimer, possibly 177^{272,273} [Eq. (107)].



²⁷⁰ S. Roffia and G. Feroci, *J. Electroanal. Chem.* **88**, 169 (1978).

²⁷¹ H. H. Rüttinger, R. Spitzner, W. Schroth, H. Matschiner, and R. Ziebig, *J. Prakt. Chem.* **323**, 33 (1981).

²⁷² C. Barry, G. Cauquis, and M. Maurey, *Bull. Soc. Chim. Fr.*, 2510 (1966).

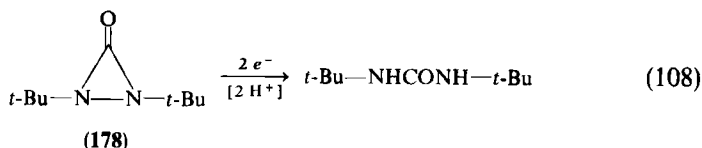
²⁷³ G. Cauquis, A. Deronzier, and D. Serve, *J. Electroanal. Chem.* **47**, 193 (1973).

The anodic oxidation of 10-phenylphenothiazine in $\text{CH}_3\text{CN}-\text{Et}_4\text{NClO}_4$ solution of pyridine gives rise to the formation of *N*-[3-(10-phenylphenothiazinyl)]pyridinium perchlorate, the parent compound, and pyridinium perchlorate.²⁷⁴ On the basis of kinetic determinations a half-regeneration mechanism was proposed.

D. COMPOUNDS WITH TWO NITROGEN ATOMS

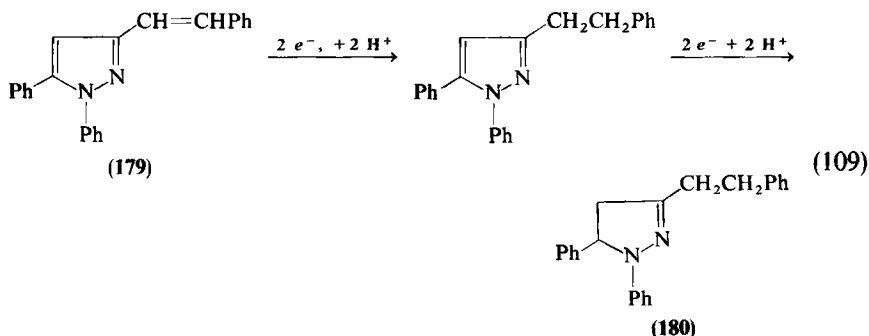
1. Diaziridines

The electrochemistry of diazirines and diaziridines was discussed in Part I.¹ Di-*tert*-butyldiaziridone (**178**) can be reduced in aprotic media in an irreversible two-electron reduction.²⁷⁵ Whereas diaziridines require acidic conditions for the splitting of the N—N bond and are electrochemically inert toward reduction in alkaline solutions, **178** is reduced in aprotic media to di-*tert*-butylurea [Eq. (108)].



2. Pyrazoles and Pyrazoline Derivatives

1,5-Diphenyl-3-styrylpyrazole (**179**) is reducible in moist DMF in two steps: reduction at the potential of the first step produces 1,5-diphenyl-3-(phenylethyl)pyrazole, whereas 1,5-diphenyl-3-(phenylethyl)- Δ^2 -pyrazoline (**180**) results from reduction at the second step²⁷⁶ [Eq. (109)].



²⁷⁴ J. F. Evans, J. R. Lenhard, and H. N. Blount, *J. Org. Chem.* **42**, 983 (1977), and references therein.

²⁷⁵ A. Fry, W. E. Britton, R. Wilson, F. D. Greene, and J. G. Pacifi, *J. Org. Chem.* **38**, 2620 (1973).

²⁷⁶ J. Grimshaw and J. Trocha-Grimshaw, *J. C. S. Perkin I*, 1275 (1973).

- 277 H. H. Adam and T. A. Joslin, *J. Electroanal. Chem.* **58**, 393 (1975).
- 278 H. H. Adam and T. A. Joslin, *J. Electroanal. Chem.* **72**, 197 (1976).
- 279 F. Pragst, *J. Prakt. Chem.* **315**, 549 (1979).
- 280 F. Pragst and B. Siefke, *J. Prakt. Chem.* **316**, 267 (1974).
- 281 F. Pragst and I. Schwertfeger, *J. Prakt. Chem.* **316**, 795 (1974).
- 282 F. Pragst and W. Jugelt, *J. Prakt. Chem.* **316**, 981 (1974).
- 283 F. Pragst, *Z. Chem.* **14**, 236 (1974).
- 284 F. Pragst and C. Böck, *J. Electroanal. Chem.* **61**, 47 (1975).
- 285 F. Pragst, H. Köppel, W. Jugelt, and F. G. Weber, *J. Electroanal. Chem.* **60**, 323 (1975).
- 286 M. Genies, *J. Electroanal. Chem.* **79**, 351 (1977).
- 287 H. H. Adam, B. D. Baigrie, and T. A. Joslin, *J. C. S. Perkin II*, 1287 (1977).
- 288 M. Genies and A. F. Diaz, *J. Electroanal. Chem.* **98**, 305 (1979).
- 289 B. D. Baigrie, T. A. Joslin, and D. W. Sopher, *J. C. S. Perkin II*, 77 (1979).
- 290 I. Tabaković and Z. Grujić, *Bull. Soc. Chim., Beograd* **47**, 339 (1982).

dimeric 3-amino-4,5-dihydro-1-[4'-(3-amino-4,5-dihydropyrazol-1-yl)]biphenyl-4-yl]pyrazole and a small amount of 3-amino-1-phenylpyrazole.²⁸⁹

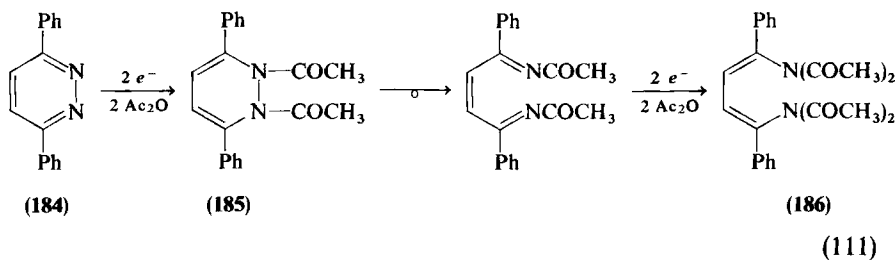
3. Imidazole Derivatives

The anodic oxidation of 2,4,5-triarylimidazole was studied in aprotic solvents.²⁹¹⁻²⁹⁵ The 2,4,5-triarylimidazole anions undergo a one-electron oxidation, forming dimeric bis-(2,4,5-triarylimidazolyls).²⁹⁴ The isomeric bisimidazolyls consist of imidazole and isoimidazole systems. The dimerization is a result of a nucleophilic attack of 2,4,5-triarylimidazole anions on the electrochemically generated 2,4,5-triarylimidazolium cations.

4. Pyridazines

The reduction of a number of pyridazines was treated in Part I¹; later electrochemical investigations²⁹⁶ confirmed that the initial reduction consumed two electrons and the primary product was suggested to be 1,2-dihydropyridazine, which tautomerized to the 1,4-dihydro derivative; hydrolysis with ring opening followed.

In aprotic media in the presence of acetic anhydride, 3,6-diphenylpyridazine (**184**) is first reduced to 1,2-diacetyl-1,2-dihydropyridazine (**185**); this is followed by cleavage of the N—N bond and further reduction to give 1,4-diphenyl-1,4-bis(diacetylamino)butadiene (**186**)²⁹⁷ [Eq. (111)]. Anodic oxidation of **186** in acetonitrile yields 3,6-diphenylpyridazine.²⁹⁸



²⁹¹ W. Sümmermann and H. Baumgärtel, *Ber. Bunsenges. Phys. Chem.* **74**, 19 (1970).

²⁹² W. Sümmermann and H. Baumgärtel, *Collect. Czech. Chem. Commun.* **36**, 575 (1975).

²⁹³ M. Libert and C. Caullet, *Bull. Soc. Chim. Fr.*, 345 (1976).

²⁹⁴ U. Lang and H. Baumgärtel, *J. Electroanal. Chem.* **78**, 133 (1977).

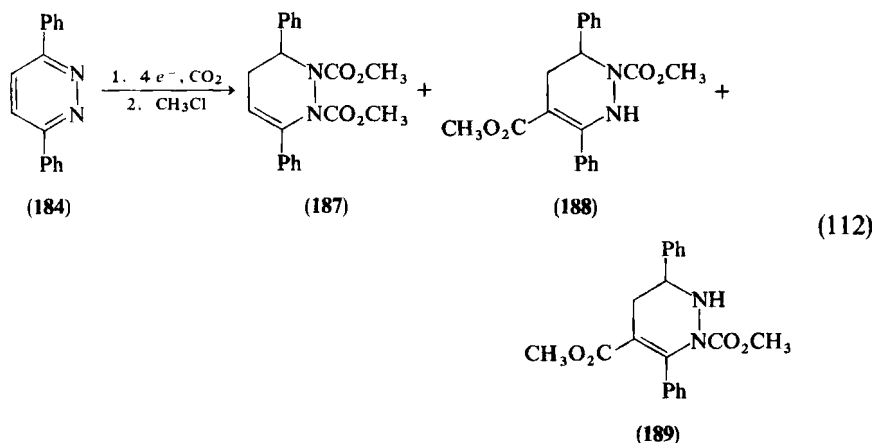
²⁹⁵ R. Hülhagen and H. Baumgärtel, *J. Electroanal. Chem.* **98**, 119 (1979).

²⁹⁶ L. N. Klatt and R. L. Rouseff, *J. Electroanal. Chem.* **41**, 411 (1973).

²⁹⁷ H. Lund and J. Simonet, *C. R. Acad. Sci., Ser. C* **277**, 1387 (1973).

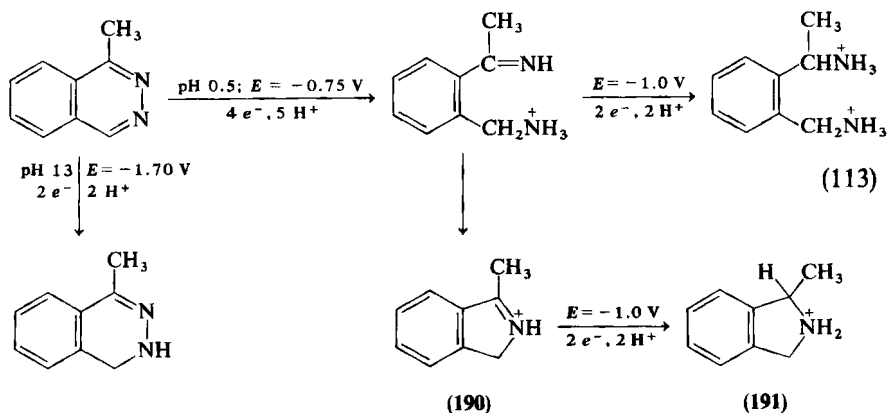
²⁹⁸ P. Martigny, H. Lund, and J. Simonet, *Electrochim. Acta* **21**, 345 (1976).

Reductive carboxylation in DMF, followed by methylation with methyl chloride, of **184** yielded a mixture of 1,2-di(methoxycarbonyl)-1,2,5,6-tetrahydro-3,6-diphenylpyridazine (**187**), 1,4-di(methoxycarbonyl)-1,2,5,6-tetrahydro-3,6-diphenylpyridazine (**188**), and 2,4-di(methoxycarbonyl)-1,2,5,6-tetrahydro-3,6-diphenylpyridazine (**189**)¹⁶ [Eq. (112)].



5. Cinnolines and Phthalazines

The reductions of cinnolines and phthalazines were discussed in Part I, Section IV,B (Ring Contractions) or V,D. 1-Methylisoinidole (**190**) has since been isolated as a hydrochloride from reduction in hydrochloric acid of 1-methylphthalazine with strict control of the potential to avoid further reduction to methylisoinidoline (**191**). Purification requires acidic conditions; the free base turned quickly to a tar^{299,300} [Eq. (113)].



²⁹⁹ H. Lund and E. T. Jensen, *Acta Chem. Scand.* **24**, 1867 (1970).

³⁰⁰ H. Lund and E. T. Jensen, *Acta Chem. Scand.* **25**, 2727 (1971).

In slightly alkaline solution 2-alkylphthalazinium cation is reduced in a one-electron reaction to a 1:1 mixture of (\pm) and meso forms of the 1,1'-dimer.²⁹⁹

6. Pyrimidines

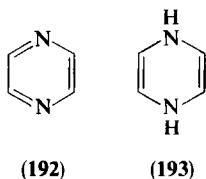
The polarographic reduction of pyrimidine was discussed in Part I,¹ and further details have been clarified.^{301,302} The first reduction is to a radical that can dimerize and accept another electron in a second step to a dihydro derivative; this may at a more negative potential be reduced to a tetrahydropyrimidine.

In Section III,B it was pointed out that 2-phenylpyrimidines did not follow the general reduction path of pyrimidines but were reduced to 2-phenylpyrroles in a four-electron ring-contraction reaction.¹⁷⁴ [Eq. (86)].

Electrochemical oxidation of uracil in methanol containing Et₄NCN gave 95% of 5-cyanouracil.³⁰³ Barbituric acid, 1-methylbarbituric acid, and 1,3-dimethylbarbituric acid are electrochemically oxidized at a pyrolytic graphite electrode at pH 1 in the presence of chloride ion.³⁰⁴ Three isolated major products were the appropriate N-methylated 5,5'-dichlorohydurilic acids, the 5,5'-dichlorobarbituric acids, and the alloxanes. 1,3-Dimethylbarbituric acid was oxidized in 1 M acetic acid at a pyrolytic graphite electrode, to give 5,6-dihydro-1,3-dimethyl-5,6-di(1',3'-dimethyl-2',4',6'-trioxypyrimid-5',5'-yl)furo[2,3-*d*]uracil (46%).³⁰⁵ Further details may be found in the book by Dryhurst.⁵

7. Pyrazines

Pyrazine **192** is reduced in acidic solution in two one-electron steps through the protonated radical to 1,4-dihydropyrazine (**193**); **192** and **193** can react with formation of two PH \cdot radicals.^{306,307} The 1,4-dihydro- (or



³⁰¹ D. Thevenot, *J. Electroanal. Chem.* **46**, 89 (1973).

³⁰² P. J. Elving, S. J. Pace, and J. E. O'Reilly, *J. Am. Chem. Soc.* **95**, 647 (1973).

³⁰³ H. Meinert and D. Cech, *Z. Chem.* **12**, 291 (1972).

³⁰⁴ S. Kato and G. Dryhurst, *J. Electroanal. Chem.* **62**, 415 (1975).

³⁰⁵ S. Kato, M. Poling, D. van der Helm, and G. Dryhurst, *J. Am. Chem. Soc.* **96**, 5255 (1974).

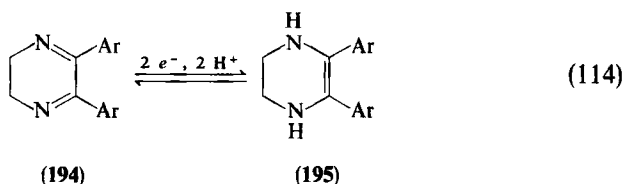
³⁰⁶ J. Swarcz and F. C. Anson, *J. Electroanal. Chem.* **114**, 117 (1980).

³⁰⁷ L. N. Klatt and R. L. Rouseff, *J. Am. Chem. Soc.* **94**, 7295 (1972).

1,2-dihydro-) pyrazine is hydrolyzed in acidic solution with ring opening and further reactions. In neutral or alkaline medium, phenyl-substituted pyrazines are reduced to the 1,4-dihydro derivatives, which tautomerize to 1,2- or 1,6-dihydro compounds. Further reduction to tetrahydro- or even hexahydropyrazines may occur.^{308,309}

1,4-Dihydropyrazines are readily reoxidized to pyrazines and are difficult to isolate³⁰⁹; reduction of **192** in aprotic medium in the presence of acetic anhydride gives 1,4-diacetyl-1,4-dihydropyrazine,^{297,310} which is the first stable 1,4-dihydropyrazine isolated. Reductive carboxylation of **192** in DMF, followed by alkylation, is also expected to produce a stable 1,4-dihydropyrazine.

2,3-Diaryl-5,6-dihydropyrazines **194** are analogous to benzil dianils³¹¹ and are reduced in aqueous solution in an analogous way; a diimine-enediamine is analogous to a dione-enediol, and the products from **194** are the expected 2,3-diaryl-1,4,5,6-tetrahydropyrazines **195**³¹⁰ [Eq. (114)].



8. Quinoxalines

The reduction of quinoxalines was discussed in Part I¹; newer investigations have confirmed the general scheme.^{312,313} The quaternized compound, 2,3-diphenyl-1-methylquinoxalinium cation, is reduced in two one-electron reductions. The first reduction results in a radical, which may be further reduced to a 1,4-dihydro derivative; this may tautomerize to 1,2-dihydro-2,3-diphenyl-1-methylquinoxaline.³¹⁴

In aprotic media, quinoxalines may be reductively acylated²⁹⁷ or carboxylated¹⁶ [Eq. (115)] and probably also reductively alkylated at the two nitrogen atoms to stable 1,4-dihydroderivatives.

³⁰⁸ J. Pinson and J. Armand, *Bull. Soc. Chim. Fr.*, 1764 (1971); J. Armand, P. Bassinet, K. Chekir, J. Pinson, and P. Souchay, *C. R. Acad. Sci., Ser. C* **275**, 279 (1972).

³⁰⁹ J. Armand, K. Chekir, and J. Pinson, *Can. J. Chem.* **52**, 3971 (1974).

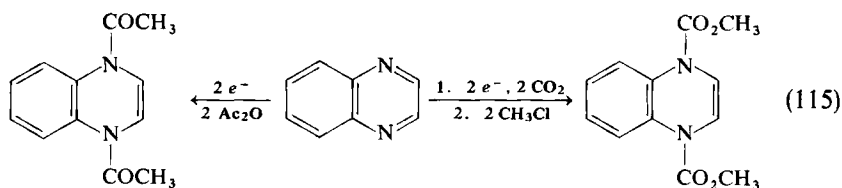
³¹⁰ R. Gottlieb and W. Pfeleiderer, *Liebigs Ann. Chem.*, 1451 (1981).

³¹¹ J. Simonet and H. Lund, *Bull. Soc. Chim. Fr.*, 2547 (1975).

³¹² J. Pinson and J. Armand, *Collect. Czech. Chem. Commun.* **36**, 585 (1971).

³¹³ M. Federonko and I. Jezo, *Collect. Czech. Chem. Commun.* **37**, 1781 (1972).

³¹⁴ J. Armand, K. Chekir, and J. Pinson, *J. Heterocycl. Chem.* **17**, 1237 (1980).



3,4-Dihydroquinoxalin-2-one exhibits two successive one-electron oxidation steps in DMF–Bu₄NClO₄.³¹⁵ Anodic dehydrogenation occurs presumably through an ECE mechanism.

9. Phenazines

Newer investigations^{316–318} have substantiated those previously published (Part I). Reductions in aprotic media in the presence of alkylating agents produced 5,10-dialkyl-5,10-dihydrophenazines.³¹⁹

The anodic oxidation of phenazine *N,N'*-dioxide at a platinum anode in benzonitrile led to the intermediate radical-cation, which dimerizes.^{320,321} 5-Substituted 5,10-dihydrophenazines are oxidized in two successive one-electron steps or one two-electron step in aqueous acetone.³²² The corresponding phenazinium salts were formed as the ultimate oxidation products.

10. Naphthyridines

As mentioned in Part I, all the naphthyridines and their mono- and diquaternary salts should be reducible, and this has now been shown. The stability of the radicals formed in acidic solution depends on pH and their structure; the symmetric naphthyridines form more stable radicals than the unsymmetric. The structures of the dimerized products have not been established.^{323–326}

³¹⁵ I. M. Sosonkin, G. N. Strogov, V. N. Charushin, and O. Chupakhin, *Khim. Geterotsikl. Soedin.*, 261 (1981) [*CA* **94**, 147502 (1981)].

³¹⁶ S. Nakamura, *Denki Kagaku* **39**, 502 (1971) [*CA* **75**, 104466 (1971)].

³¹⁷ S. Nakamura and T. Yoshida, *Denki Kagaku* **40**, 714 (1972) [*CA* **78**, 91765 (1973)].

³¹⁸ J. Kulys and A. Malinauskas, *Liet. TSR Mokslu Akad. Darb., Ser. B*, 41 (1979) [*CA* **91**, 131180 (1979)].

³¹⁹ D. K. Root, R. D. Pendarvis, and W. Smith, *J. Org. Chem.* **43**, 778 (1978).

³²⁰ A. Stüwe and H. Baumgärtel, *Ber. Bunsenges. Phys. Chem.* **78**, 320 (1974).

³²¹ A. Stüwe and H. Baumgärtel, *Ber. Bunsenges. Phys. Chem.* **78**, 309 (1974).

³²² I. N. Borukhova, V. F. Gryazev, I. A. Yarrisheva, and Z. V. Pushkareva, *Khim. Geterotsikl. Soedin.*, 548 (1976) [*CA* **85**, 20386 (1976)].

³²³ E. Laviron and L. Roullier, *C. R. Acad. Sci., Ser. C* **274**, 1489 (1972).

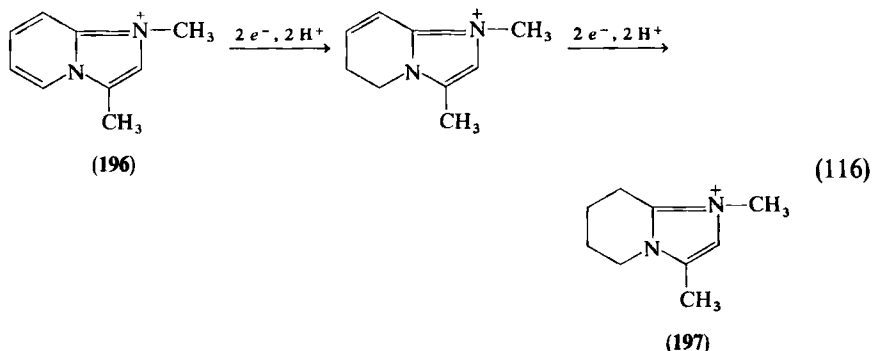
³²⁴ L. Roullier and E. Laviron, *Electrochim. Acta* **21**, 421 (1976).

³²⁵ L. Roullier and E. Laviron, *Electrochim. Acta* **22**, 669 (1977).

³²⁶ L. Roullier and E. Laviron, *Electrochim. Acta* **23**, 773 (1978).

11. Imidazopyridinium and Pyrrolopyrimidinium Salts

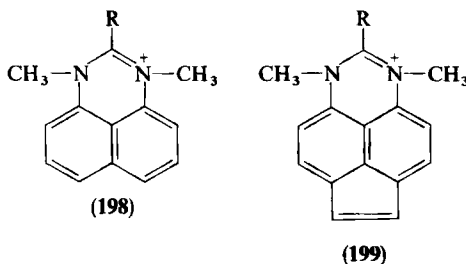
The pyridine ring in 1,3-dimethylimidazo[1,2-*a*]pyridinium salts (**196**) is reduced in two two-electron steps in aqueous media to a dihydro- and then to a tetrahydro compound **197** [Eq. (116)],



whereas the pyrrolopyrimidinium cations are reduced in two one-electron steps analogously to pyrimidine.³²⁷

12. Perimidinium Ions

1,3-Dimethylperimidinium perchlorate (**198**) is reduced polarographically in two one-electron waves; the first gives a rather stable radical.³²⁸ 1,3-Dimethyl-2-phenylperimidinium perchlorate undergoes a single two-electron reduction to the dihydro derivative. Aceperimidinium (**199**) ions behave similarly.

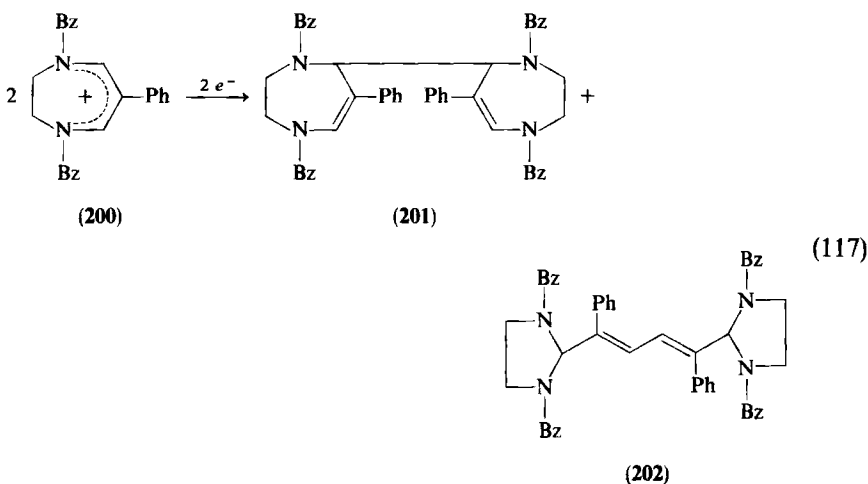


³²⁷ A. V. Lizogub, Z. N. Timofeeva, M. L. Alexandrova, A. V. El'tsov, and E. G. Petrova, *Zh. Obshch. Khim.* **43**, 2280 (1973) [*CA* **80**, 47906 (1974)].

³²⁸ A. V. Lizogub, A. F. Pozharskii, and V. I. Sokolov, *Zh. Obshch. Khim.* **46**, 680 (1976) [*CA* **84**, 179308 (1976)].

13. Diazepines and Benzo Derivatives

The reduction in DMF of 6-phenyl-2,3-dihydro-1,4-diazepinium cation (**76**) to 4,5-dihydro-1,8-diphenyl-3*H*-pyrrolo[1,2-*d*][1,4]diazepine^{133,134,329} (**77**) was discussed in Section III,A. The initial reduction is of the cation to the neutral radical, which dimerizes in a fast reaction. When both nitrogen atoms are substituted with benzyl groups (**200**), the follow-up reaction takes another route, inasmuch as an elimination of ethylenediamine after the initial dimerization is not possible in such a case. The meso- and (\pm)-5,5'-dimers (**201**) and a diimidazolidinylbutadiene (**202**) was isolated from reduction of **200** in DMF at a mercury or platinum electrode³³⁰⁻³³² [Eq. (117)].



The reduction of benzo-1,4-diazepines was discussed in Part I, and the reduction of 3-hydroxy derivatives³³³⁻³³⁵ will be treated in Section V,B. Many papers and a review³³⁶ have treated the electroanalytical determination of benzo-1,4-diazepines.

³²⁹ D. Lloyd, C. A. Vincent, D. J. Walton, J. P. Declercq, G. Germain, M. van Meerssche, *J. C. S. Chem. Commun.*, 499 (1978).

³³⁰ J. P. Declercq, G. Germain, and M. van Meerssche, *Acta Crystallogr., Sect. B* **B35**, 1175 (1979).

³³¹ M. van Meerssche, G. Germain, and J. P. Declercq, *Acta Crystallogr., Sect. B* **B36**, 1418 (1980).

³³² D. Lloyd, C. A. Vincent, D. J. Walton, J. P. Declercq, G. Germain, and M. van Meerssche, *Bull. Soc. Chim. Belg.* **88**, 113 (1979).

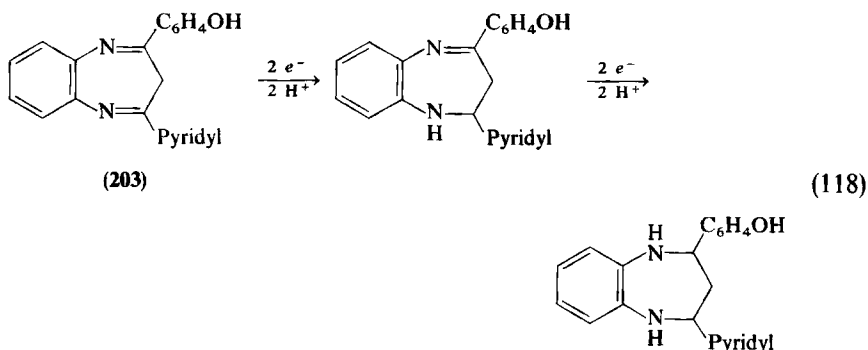
³³³ B. Maupas and M. B. Fleury, *Electrochim. Acta* **26**, 399 (1981).

³³⁴ B. Maupas and M. B. Fleury, *Electrochim. Acta* **27**, 141 (1982).

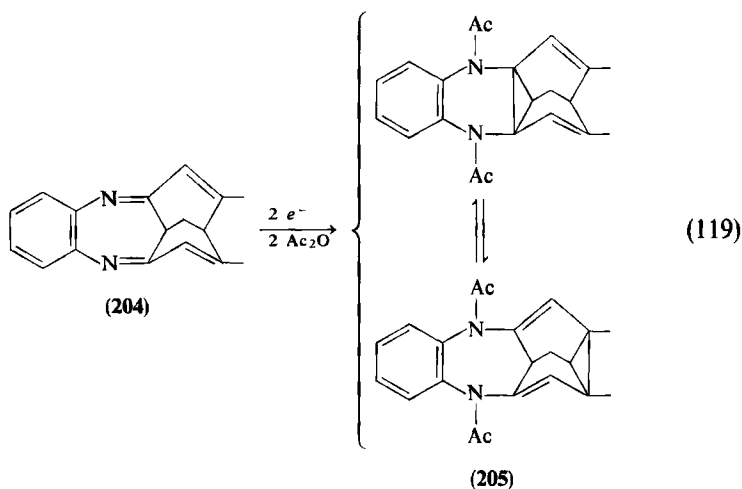
³³⁵ H. Oelschläger and F. I. Sengün, *Chem. Ber.* **108**, 3303 (1975).

³³⁶ M. A. Brooks and J. A. F. DeSilva, *Talanta* **22**, 849 (1975).

Benzo-1,5-diazepines, such as **203**, are reduced in a H_2O –DMF mixture in two steps.³³⁷ It has been suggested that the two steps correspond to the saturation of the two $\text{C}=\text{N}$ bonds [Eq. (118)]. Possibly the second step is caused by or also involves cleavage of the $\text{C}-\text{N}$ bond α to the 4-pyridyl group.



Bridged 1,5-benzodiazepines (**204**), prepared by condensation of *o*-phenylenediamine with 4,6-dimethylbicyclo[3.3.1]nona-3,6-diene-2,8-dione, give barbaralanes (**205**) on electrochemical reduction in acetonitrile in the presence of acetic anhydride³³⁸ [Eq. (119)]. The reaction is akin to the reduction of acetylacetone in which cyclopropane derivatives have been formed.^{339,340}



³³⁷ K. Butkiewicz, *J. Electroanal. Chem.* **90**, 271 (1978).

³³⁸ J. M. Mellor, B. S. Pons, and J. H. A. Stibbard, *J. C. S. Chem. Commun.*, 761 (1979).

³³⁹ T. J. Curphey, C. W. Amelotti, T. P. Layloff, R. L. McCartney, and J. H. Williams, *J. Am. Chem. Soc.* **91**, 2817 (1969).

³⁴⁰ A. D. Thomsen and H. Lund, *Acta Chem. Scand.* **25**, 1576 (1971).

E. COMPOUNDS WITH TWO NITROGEN AND ONE OXYGEN OR SULFUR ATOMS

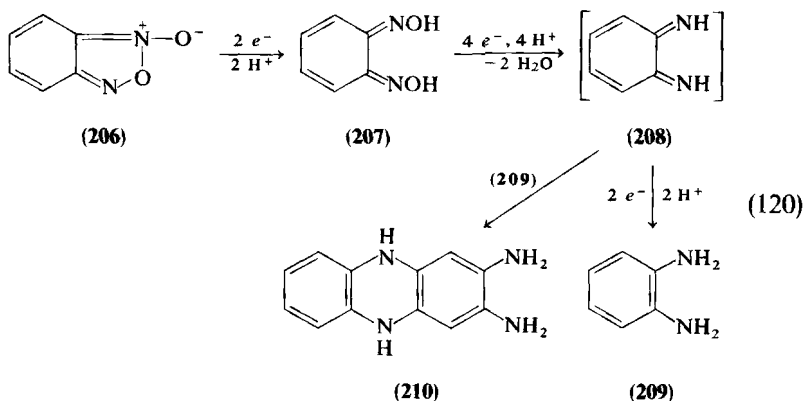
Oxadiazoles, benzofurazans, sydnone, thiadiazoles, and benzothia- and seleno-diazoles were discussed in Part I.

1. 1,3,4-Oxadiazoles

The reduction of oxadiazoles^{262,263,341} has been investigated polarographically in aprotic media. Two one-electron waves have been found for 2,5-diphenyl-1,3,4-oxadiazole, whereas others give more waves, depending on the substituents. The course of the electrode reactions has not been established.

2. Benzofuroxans

Reduction of benzofuroxan (206)³⁴² in neutral and alkaline solution first gives *o*-benzoquinonedioxime (207), which, as other oximes, is reduced with cleavage of the N—O bond to the diimine (208). The diimine then undergoes a two-electron reduction to *o*-phenylenediamine (209) or condenses with 209 to 2,3-diamino-9,10-dihydrophenazine 210 [Eq. (120)].



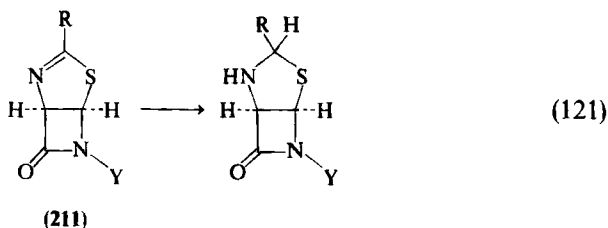
3. Thiazolineazetidinones

The C=N bonds in thiazolineazetidinones (211) may be saturated in high yield by using electrochemical reduction in a two-phase system (aqueous

³⁴¹ G. L. Smith and J. W. Rogers, *J. Electrochem. Soc.* **118**, 1089 (1971).

³⁴² C. D. Thompson and R. T. Foley, *J. Electrochem. Soc.* **119**, 177 (1972).

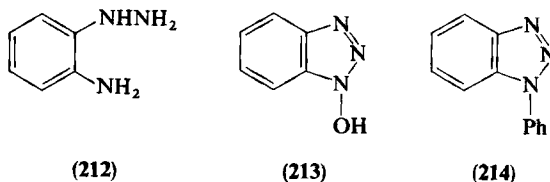
$\text{HClO}_4\text{-CH}_2\text{Cl}_2$) with vigorous stirring [Eq. (121)]. The direction of the current was changed every 30 sec by means of a commutator. The labile thiazoline and β -lactam ring systems were not affected by HClO_4 in the two-phase system.³⁴³



F. COMPOUNDS WITH THREE NITROGEN ATOMS

1. Benzotriazoles

The reduction of benzotriazole (119) to 2-aminophenylhydrazine (212), followed by condensation with orthoesters¹⁷⁵ to benzo-1,2,4-triazines was mentioned in Section III.C. The reduction of 1-hydroxybenzotriazoles³⁴⁴ (213) via 119 to 212 was suggested to involve electrochemically produced hydrogen rather than a direct electron transfer. This seems improbable inasmuch as it occurs at a mercury cathode with very little catalytic activity. Furthermore, 1-phenylbenzotriazole³⁴⁵ (214) gives a four-electron diffusion-controlled polarographic wave, and both 214 and 119¹⁷⁵ take up 4 F/mol in preparative reductions.



2. Triazines

The reduction of 3,5,6-triphenyl-1,2,4-triazine (114)³⁴⁶ to the dihydro derivative (first wave) and then to a mixture of a tetrahydro derivative (116) and

³⁴³ S. Torii, H. Tanaka, M. Satsuki, T. Siroi, N. Saitoh, M. Sasaoka, and J. Nokami, *Chem. Lett.*, 1575 (1981).

³⁴⁴ J. Volke, V. Volkova, and H. Oelschläger, *Electrochim. Acta* **25**, 1177 (1980).

³⁴⁵ H. Lund, to be published.

³⁴⁶ J. Pinson, J.-P. M'Packo, N. Vinot, J. Armand, and P. Bassinet, *Can. J. Chem.* **50**, 1581 (1972).

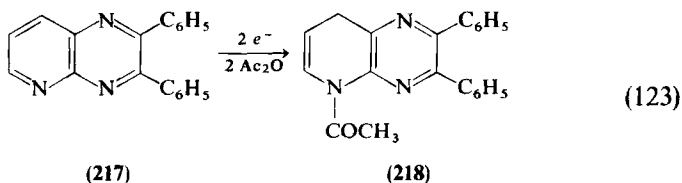
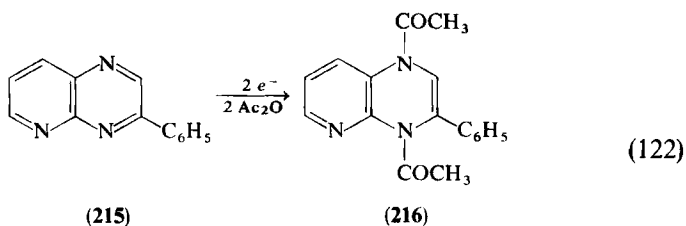
2,4,5-triphenylimidazole (**115**) (second wave) was mentioned in Section III,B [Eq. (85)].

In acetonitrile, reduction potentials have been determined for 22 substituted 1,2,4-triazines.³⁴⁷ 3,5-Disubstituted and 3,5,6-trisubstituted triazines show reversible behavior, with the formation of the corresponding anion-radicals; the anion-radicals from 5-unsubstituted triazines are less stable and react probably by dimerization.

In acid solution 1,3,5-triazines are reduced polarographically in a two-electron reduction.³⁴⁸

3. Pyridopyrazines

Pyrido[2,3-*b*]pyrazines are reduced^{349,350} in aqueous-ethanolic medium initially to the 1,4-dihydro derivative. Just as in the reduction of quinoxalines, the dihydropyridopyrazines may isomerize to 3,4-dihydro derivatives, but, surprisingly, some also isomerize to 5,8-dihydropyridopyrazines, which add ethanol to give a tetrahydro derivative. In acetonitrile in the presence of acetic anhydride, 3-phenylpyrido[2,3-*b*]pyrazine (**215**) is reduced to the 1,4-diacetyl-1,4-dihydro derivative **216** [Eq. (122)], whereas the 2,3-diphenylpyrido[2,3-*b*]pyrazine (**217**) under these conditions gives 5-acetyl-5,8-dihydropyridopyrazine (**218**) [Eq. (123)].



³⁴⁷ T. Troll, *Electrochim. Acta* **27**, 1311 (1982).

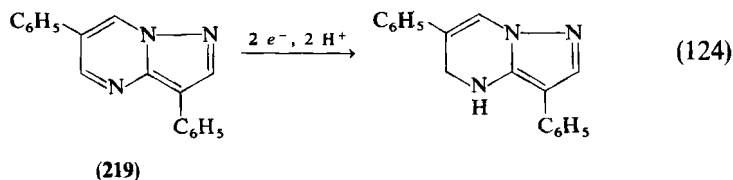
³⁴⁸ G. S. Supin, M. Ya. Fainshraiber, I. A. Mel'nikov, N. N. Mel'nikov, and T. N. Motorova, *Zh. Obshch. Khim.* **47**, 2338 (1977) [*CA* **88**, 29579 (1978)].

³⁴⁹ J. Armand, K. Chekir, and J. Pinson, *C. R. Acad. Sci., Ser. C* **284**, 391 (1977).

³⁵⁰ J. Armand, K. Chekir, and J. Pinson, *Can. J. Chem.* **56**, 1804 (1978).

4. *Pyrazolo[1,5-a]pyrimidines*

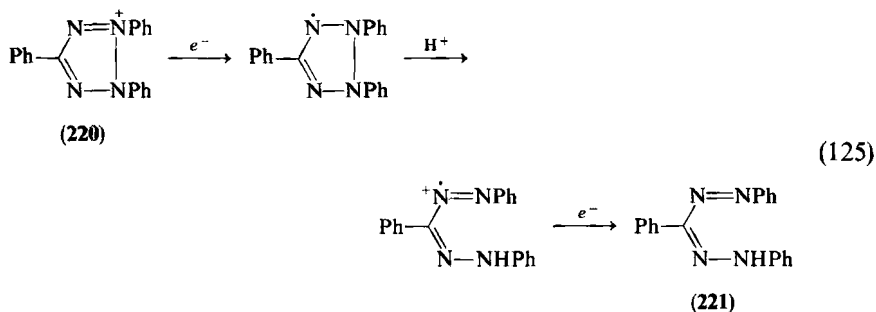
3,6-Diphenylpyrazolo[1,5-*a*]pyrimidine (**219**) has been³⁵¹ reduced in an acid solution, pH 1.15, of 50% acetonitrile, in a two-electron reduction to the 4,5-dihydro derivative [Eq. (124)]. This compound is also obtained from the 7-aminopyrazolopyrimidine in a four-electron reduction, in which **219** can be detected as an intermediate.



G. COMPOUNDS WITH FOUR OR FIVE NITROGEN ATOMS

1. *Tetrazolium Salts*

The electrochemistry of tetrazolium salts (**220**) in aqueous media was discussed in Part I. In a strictly aprotic medium **220** gives a reversible one-electron reduction to a radical with a lifetime longer than the time scale of CV.³⁵² In moist acetonitrile the reaction becomes a two-electron reduction similar to that in aqueous, basic media; a formazan (**221**) is formed [Eq. (125)].



³⁵¹ C. Bellec, P. Maitte, J. Armand, and J. Pinson, *Can. J. Chem.* **59**, 2826 (1981).

³⁵² I. Tabaković, M. Trkovnik, and Z. Grujić, *J. C. S. Perkin II*, 166 (1979).

2. Tetrazines

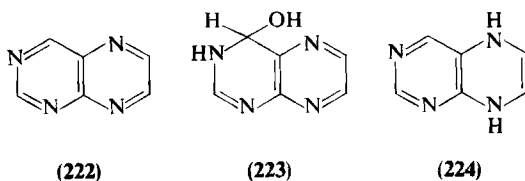
1,2,4,5-Tetrazines, investigated by cyclic voltammetry in acetonitrile, give an uncomplicated, reversible reduction to an anion-radical, which is stable on the time scale of CV.³⁴⁷

3. Purines and Pteridines

The electrolytic reduction of purines and pteridines in aqueous acidic medium was treated in Part I and is discussed in Ref. 5. In aprotic media 6-substituted purines are reduced to a dimer³⁵³ in a one-electron reaction, whereas in the presence of a proton donor the reduction resembles that in aqueous media.³⁰²

7,9-Dimethylpurinium salts in the first step give the 1,6-dihydro-7,9-dimethylpurinium cation and in a second the 1,2,3,6-tetrahydro derivative³⁵⁴; in acetonitrile the imidazolinium ring is reduced. 7-Methylguanisine, on the other hand, is reported to be reduced in the imidazole ring in aqueous solution to a 7,8-dihydro derivative.³⁵⁵

Pteridine (222) is analogous to quinazoline in that it adds water reversibly to the nucleus; 222 then forms 3,4-dihydro-4-hydroxypteridine (223). In contrast to hydrated quinazoline, 223 is reducible; both 222 and 223 are reducible in the pyrazine ring to the 5,8-dihydro derivative. Whereas 222 is reversibly reduced, 223 is reduced in an irreversible reaction. The electrochemical behavior of pteridine is further complicated by the reaction of 5,8-dihydropteridine (224) with 222 to a reducible dimer.^{5,356}



5,6,7,8-Tetrahydropteridines are oxidized to quinonoid dihydropteridines, the structures of which are not yet established.³⁵⁷

³⁵³ K. S. V. Santhanam and P. J. Elving, *J. Am. Chem. Soc.* **96**, 1653 (1974).

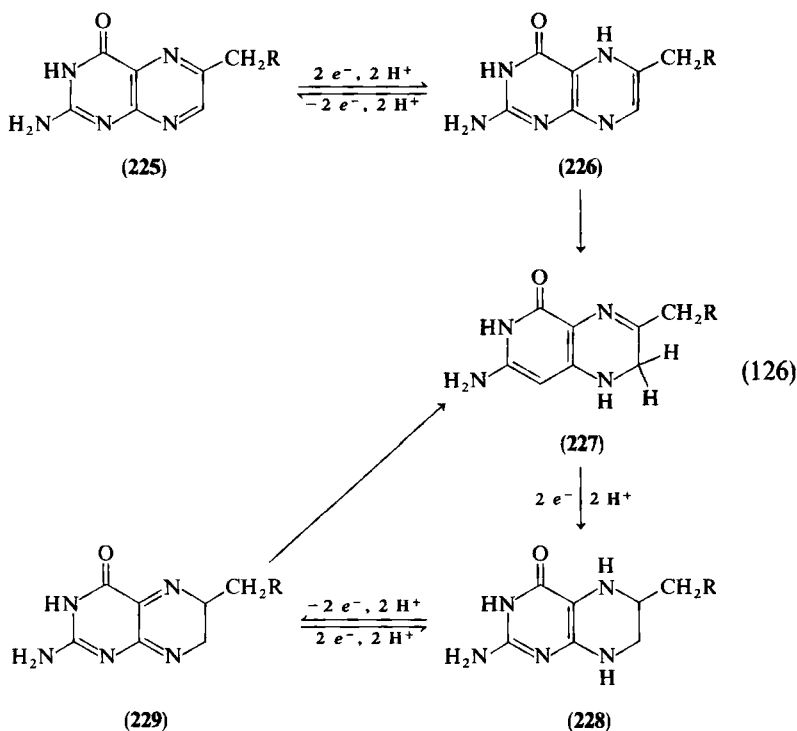
³⁵⁴ Z. N. Timofeeva, L. S. Tikhonova, Kh. L. Muravich-Aleksandr, and A. V. El'tsov, *Zh. Obshch. Khim.* **44**, 2013 (1974) [*CA* **82**, 16152 (1975)].

³⁵⁵ J. M. Sequaris and J. A. Reynaud, *J. Electroanal. Chem.* **63**, 207 (1975).

³⁵⁶ D. L. McAllister and G. Dryhurst, *J. Electroanal. Chem.* **59**, 75 (1975).

³⁵⁷ D. Ege-Serpkenci and G. Dryhurst, *Bioelectrochem. Bioenerg.* **9**, 175 (1982).

Pteridones behave electrochemically akin to quinoxaline, the pyrazine ring being reduced. In the first, reversible step of 6-methyl-2-amino-4(3*H*)-pteridone (**225**; R = H), a 5,8-dihydro derivative (**226**) is formed, which in a pH-dependent reaction tautomerizes to the more stable 7,8-dihydro compound **227**; **227** is reduced in acidic and neutral solution to the 5,6,7,8-tetrahydro derivative **228**, which may be oxidized to a quinonoid dihydro compound (**229**); **227** is formed on tautomerization of **229**^{358–362} [Eq. (126)].



Pteridone redox couples (**226**–**225** and **229**–**228**) have been used as mediators in electron-transfer reactions to large biological molecules.³⁶³

Folic acid [**225**: R = NHC₆H₄CONHCH(COOH)(CH₂)₂COOH] in acidic solution gives 7,8-dihydrofolic acid (**227**).³⁵⁹ In neutral medium with low

³⁵⁸ H. Lund, in "Chemistry and Biology of Pteridines" (W. Pfeleiderer, ed.), p. 645. de Gruyter, Berlin, 1975.

³⁵⁹ K. Kretzschmar and W. Jaenicke, *Z. Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **26B**, 225, 999 (1971).

³⁶⁰ S. Kwee and H. Lund, *Biochim. Biophys. Acta* **297**, 285 (1973).

³⁶¹ R. Raghavan and G. Dryhurst, *J. Electroanal. Chem.* **129**, 189 (1981).

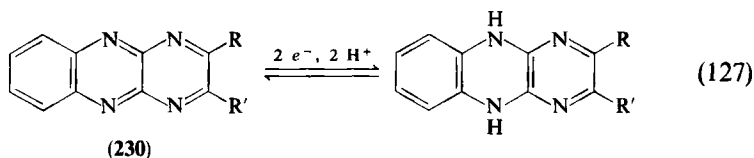
³⁶² L. G. Karber and G. Dryhurst, *J. Electroanal. Chem.* **136**, 271 (1982).

³⁶³ S. Kwee and H. Lund, *Bioelectrochem. Bioenerg.* **1**, 87 (1974).

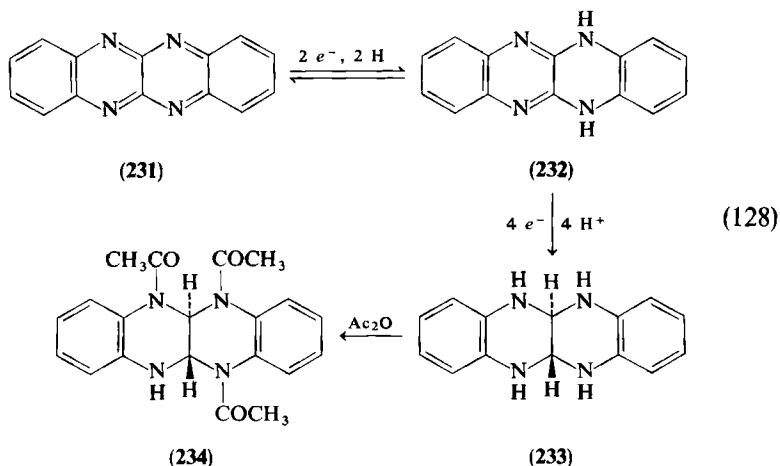
buffer capacity, it is possible to reduce 7,8-dihydrofolic acid to the 5,6,7,8-tetrahydrofolic acid³⁶⁴; in acid solution 7,8-dihydrofolic acid is reductively cleaved to **227** ($R = H$).³⁵⁹

4. Pyrazinopyrazines and Benzo Derivatives

Pyrazino[2,3-*b*]pyrazines³⁶⁵ and pyrazino[2,3-*b*]quinoxalines³⁶⁶ (**230**) are reduced similarly to pyrazines and quinoxalines to the 1,4- and 5,10-dihydro derivatives, respectively [Eq. (127)], with which they form reversible systems. 5,10-Dihydropyrazinoquinoxaline gives an ill-defined wave near the background discharge, but the structure of the product is unknown.



In aprotic medium (acetonitrile), quinoxalino[2,3-*b*]quinoxaline (**231**) undergoes two reversible reductions to an anion-radical and further to a dianion.³⁶⁷ In 1:1 H_2O -DMF **231** gives a two-electron wave followed by a four-electron wave. The first reduction leads to 5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (**232**), whereas the second reduction in a four-electron reaction leads to the 5,5a,6,11,11a,12-hexahydro derivative (**233**). On heating with acetic anhydride a triacetyl derivative (**234**) is obtained³⁶⁷ [Eq. (128)].



³⁶⁴ S. Kwee and H. Lund, *J. Electroanal. Chem.* **104**, 441 (1979).

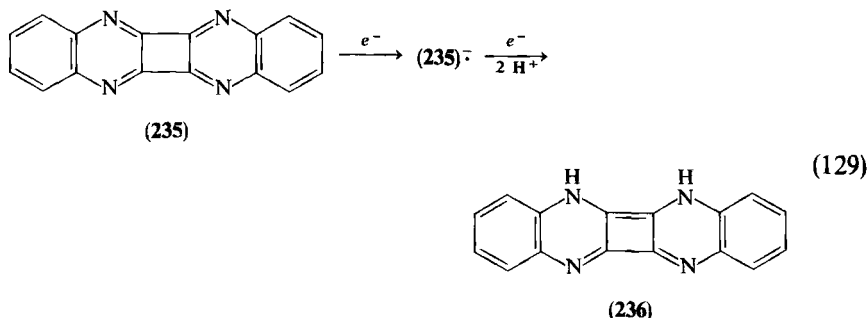
³⁶⁵ J. Armand, K. Chekir, and J. Pinson, *C. R. Acad. Sci., Ser. C* **284**, 391 (1977).

³⁶⁶ J. Armand, L. Boulares, K. Chekir, and C. Bellec, *Can. J. Chem.* **59**, 3237 (1981).

³⁶⁷ J. Armand, L. Boulares, C. Bellec, and J. Pinson, *Can. J. Chem.* **60**, 2797 (1982).

5. Cyclobutadiquinoxaline

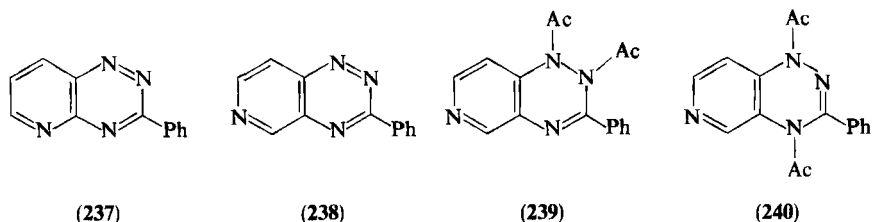
Cyclobuta[1,2-*b*:3,4-*b'*]diquinoxaline (**235**) is reduced in aprotic media in two steps through a radical-anion to a dianion that is protonated to the 5,6-dihydro derivative **236**^{368,369} [Eq. (129)].



6. Pyrido-as-triazines

In aqueous-organic medium (pH 2–13) 3-phenylpyrido[3,2-*e*]-*as*-triazine (**237**) and 3-phenylpyrido[3,4-*e*]-*as*-triazine (**238**) are reduced³⁷⁰ reversibly to the 1,4-dihydro derivatives, and in this respect are analogous to 1,2,4-benzotriazines.³⁷¹

In acetonitrile, **237** and **238** are reduced in two one-electron steps through the anion-radical to the dianion; in the presence of acetic anhydride, **238** forms a mixture of 1,2-diacetyl-1,2-dihydro-3-phenylpyrido[3,4-*e*]-*as*-triazine (**239**) and the 1,4-diacetyl-1,4-dihydro derivative (**240**). On heating of the kinetically controlled product, **239** rearranges to the thermodynamically more stable **240**.³⁷⁰



³⁶⁸ S. Hünig and H. Pütter, *Chem. Ber.* **110**, 2524, 2532 (1977).

³⁶⁹ K. Hesse, S. Hünig, H. J. Bestmann, G. Schmid, E. Wilhelm, G. Seitz, R. Matusch, and K. Mann, *Chem. Ber.* **115**, 795 (1982).

³⁷⁰ J. Armand, K. Chekir, N. Ple, G. Queguiner, and M. P. Simonnin, *J. Org. Chem.* **46**, 4754 (1981).

³⁷¹ S. Kwee and H. Lund, *Acta Chem. Scand.* **23**, 274 (1969).

7. Porphins

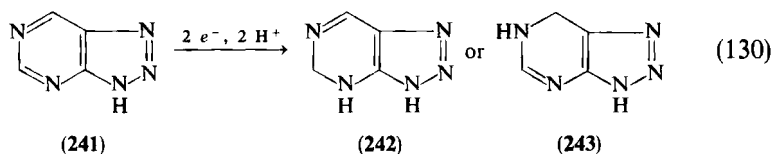
A number of dimeric metalloporphyrins, in which the two porphyrin rings are constrained to lie parallel to one another by two amide bridges of varying length, have been tested for catalytic activity toward the electroreduction of dioxygen to water rather than to hydrogen peroxide in aqueous, acidic electrolytes. An electrode material at which a rapid four-electron reduction of dioxygen to water proceeded near the reversible potential would be an important advance in fuel-cell technology. The dicobaltporphyrin linked by four-atom bridges produced a catalyzed reduction almost exclusively to water and at rather positive potentials.³⁷²

The reactivity of radical-cations of porphins with various nucleophiles has been studied; the reaction afforded the corresponding meso-substituted porphins³⁷³⁻³⁷⁵ or substitution in the β -position of the pyrrole rings in the porphins.³⁷⁶

Electrochemical oxidation in DMF of Zn-octaethylporphin in the presence of cyanide at 0.42 V (SCE) gives a quantitative yield of the cyano-octaethylporphyrin; at more positive potentials, di-, tri-, and tetracyano-octaethylporphyrins may be obtained.³⁷⁷

8. Pyrimidotriazole

Pyrimidotriazole (**241**) is reported³⁷⁸ to be reduced in aqueous solution in a two-electron reduction to the 4,5-dihydro derivative **242**. In view of the reduction route of purine (Part I), it seems more likely that the product is the 6,7-dihydro derivative **243** [Eq. (130)].



³⁷² J. P. Collman, P. Denisevich, Y. Konai, M. Marrocco, C. Koval, and F. C. Anson, *J. Am. Chem. Soc.* **102**, 6027 (1980); D. A. Buttry and F. C. Anson, *J. Am. Chem. Soc.* **106**, 59 (1984).

³⁷³ G. H. Barnet and K. M. Smith, *J. C. S. Chem. Commun.*, 722 (1974).

³⁷⁴ B. Evans, K. M. Smith, S. Besecke, and J.-H. Fuhrhop, *Tetrahedron Lett.*, 4009 (1976).

³⁷⁵ S. Besecke, G. H. Barnet, B. Evans, K. M. Smith, and J.-H. Fuhrhop, *Angew. Chem.* **88**, 616 (1976).

³⁷⁶ A. G. Padilla, W. Shi Ming, and H. J. Shine, *J. C. S. Chem. Commun.*, 236 (1976).

³⁷⁷ H. J. Callot, L. Lonati, and M. Gross, *Tetrahedron Lett.* **21**, 3281 (1980).

³⁷⁸ L. Kittler and H. Berg, *J. Electroanal. Chem.* **16**, 251 (1968).

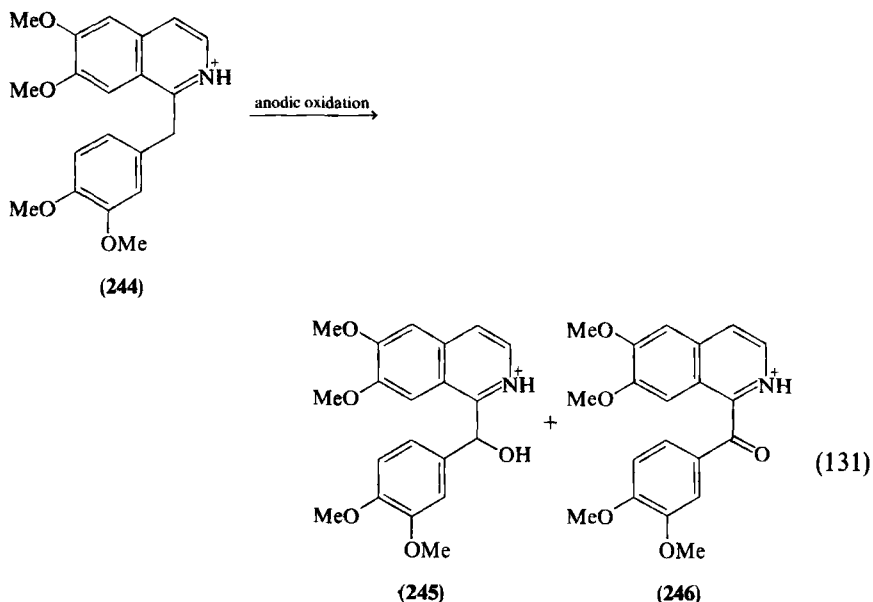
V. Electrolysis of Substituted Heterocycles

A. ALKYL AND ALKENYL SUBSTITUENTS

Alkyl derivatives of heterocyclic compounds may be oxidized to carboxylic acids, for example, methylpyridines and methylpyridine *N*-oxides by superoxide ions, generated electrochemically in DMF.⁵⁷

Anodic oxidation is a one-step method for the selective *N*-dealkylation of unstable drugs under mild conditions,³⁷⁹ e.g., lisuridine, diazepam, methysergide, and imipramine in MeOH–NaClO₄–NaOH under controlled-potential conditions gave *N*-dealkylated products (15–35%). Electrochemical oxidation of amines is initiated by electron transfer from the substrate to the anode to give immonium ions as intermediates; these then are hydrolyzed to an amine and a carbonyl compound. The similar pattern for anodic and liver microsomal *N*-dealkylation suggests similar mechanisms.

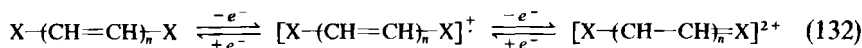
Anodic oxidation of papaverine (**244**) in an aqueous medium at pH 3–7, using a divided cell, gave papaverinol (**245**) and papaveraldine (**246**) in 40–60% and 10–20% yield, respectively.³⁸⁰ Oxidation of **244** in an undivided cell resulted in better yield (70–75%) of **245** [Eq. (131)].



³⁷⁹ T. Shono, T. Toda, N. Oshino, *Drug. Metab. Dispos.* **9**, 481 (1981) [*CA* **95**, 197126 (1981)].

³⁸⁰ N. A. Prikhodko, M. Zh. Zhurinov, and M. Ya. Fioshin, *Elektrokhimiya* **16**, 1278 (1980) [*CA* **93**, 157652 (1980)].

Various electrochemical methods have been applied to the study of two-step and even multistep redox systems, which can be envisaged as derivatives of the general structures covered by Eq. (132)



in which the three oxidation levels are separated by the redox potentials E_1 and E_2 .³⁸¹⁻³⁸³ The end groups X are a part of a heterocyclic system (pyridine, quinoline, indole, benzoxazole, benzthiazole, etc.). The stability of the semiquinoid radical-cation decreases with increasing length of the polyene bridge.

B. HYDROXYL DERIVATIVES

Heterocyclic hydroxyl derivatives can be divided into two groups according to whether or not the hydroxyl group is exocyclic. Heterocyclic compounds having a hydroxyl substituent in the ring can have hydroxy or oxo tautomeric forms, and in many cases the oxo form is predominant. Nevertheless, regardless of the position of the prototropic equilibria the compounds will be treated under this heading.

1. Hydroxyl Groups Attached to a Substituent

The reductive cleavage of the C—O bond in 2- and 4-substituted hydroxymethylpyridines was mentioned in Part I. The optically active 1-(4-pyridyl)-alkanols are reduced in good yield to the optically inactive alkylpyridine, whereas the 2-substituted derivatives were reduced in lower yield to the optically active alkylpyridine (and some tetrahydropyridine derivatives).^{384,385} The difference in behavior was explained by orientation of the adsorbed protonated pyridine, allowing contact between the electrode and the 2-substituent, but not the 4-substituent. This model was used in later work; however, not excluded was the possibility that the higher stability of the *p*-quinonoid dihydropyridine intermediate, compared to the *o*-quinonoid dihydropyridine, played a role in the relative ease of reduction of the 4- and 2-substituted pyridines.

³⁸¹ S. Hünig and H.-C. Steinmetzer, *Liebigs Ann. Chem.*, 1060 (1976).

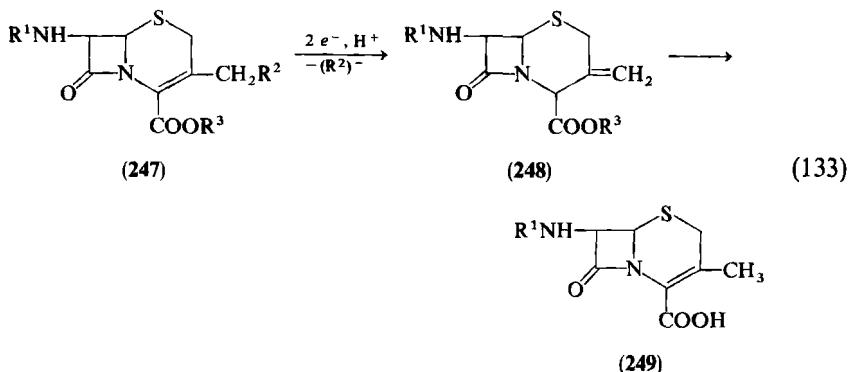
³⁸² M. Horner, S. Hünig, and H. Pütter, *Electrochim. Acta* **27**, 205 (1982).

³⁸³ S. Hünig, D. Scheutzow, H. Schlaf, and H. Pütter, *Liebigs Ann. Chem.*, 1436 (1974).

³⁸⁴ T. Nonaka, T. Ota, and T. Fuchigami, *Bull. Chem. Soc. Jpn.* **50**, 2965 (1977).

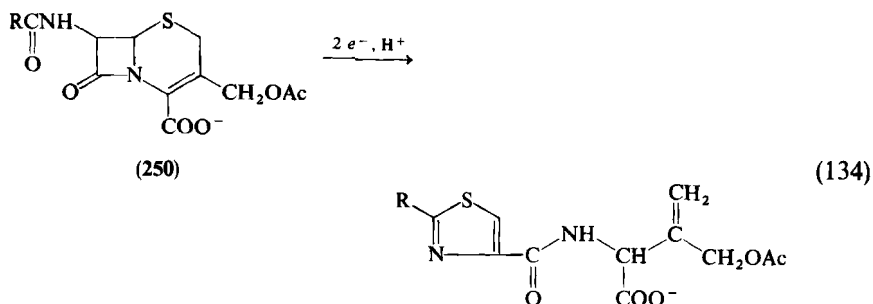
³⁸⁵ T. Nonaka, T. Kato, T. Fuchigami, and T. Sekine, *Electrochim. Acta* **26**, 887 (1981).

Allyl derivatives can also be reductively cleaved in neutral or acidic media. An example is the reduction of cephalosporanic acid derivatives (**247**; $R^2 = \text{CH}_3\text{COO}$) to the corresponding 3-methylenecepham derivatives (**248**), which could be isomerized to the 3-methyl derivatives (**249**)^{386,387} [Eq. (133)].



The double bond shift is explained in terms of a kinetically controlled protonation of the anion formed in an ECE process; the anion would have the highest negative charge α to the ester group. Such a double bond shift seems to be rather general also for the indirect reduction of allyl alcohols.³⁸⁸

The loss of a heteroatom-bonded substituent from the allyl position seems rather general; it could thus be expected that a cleavage of the C—S bond in **250** with ring opening took place as a competitive pathway to the loss of the acetoxy group; this occurs in a basic, nonbuffered medium, cleavage of the four-membered ring and a new ring closure to a thiazole follows³⁸⁹ [Eq. (134)].



³⁸⁶ M. Ochiai, O. Aki, A. Morimoto, T. Okada, K. Shinozaki, and Y. Asahi, *Tetrahedron Lett.*, 2341 (1972).

³⁸⁷ M. Ochiai, O. Aki, A. Morimoto, T. Okada, K. Shinozaki, and Y. Asahi, *J. C. S. Perkin I*, 258 (1974).

³⁸⁸ T. Lund and H. Lund, *Acta Chem. Scand., Ser. B* **B38** (1984).

³⁸⁹ D. A. Hall, D. M. Berry, and C. J. Schneider, *J. Electroanal. Chem.* **80**, 155 (1977).

dimerization of the primarily formed anion-radical is followed by an intramolecular substitution reaction in which the glycol-like dimer formed an epoxide ring; the (\pm)/meso ratio of the diastereomers was 1.63.³⁹⁰

Reduction of *N*-phenylphthalimide in dry acetonitrile containing an excess of chlorotrimethylsilane gave the 1,3-bis(trimethylsilyloxy)isoindole in a two-electron reaction.³⁹¹

b. *Derivatives of Pyrimidine.* In DMSO, 2-pyrimidone³⁹² is reduced reversibly to the anion-radical, which abstracts a proton from the parent compound; the neutral radical dimerizes rapidly. On addition of strong acid, the protonated pyrimidone is reduced to the neutral radical, which dimerizes. Thymine³⁹³ and uracil³⁹⁴ behave similarly.

c. *Derivatives of Quinazoline.* 4-Quinazoline is reduced in neutral and weakly alkaline solution to a radical that may either be reduced further to 1,2,3,4-tetrahydro-4-quinazoline or dimerize at C-2.³⁹⁵

d. *Derivatives of Pyridopyrimidine.* 2,6-Dimethyl-3-ethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine is reduced at a mercury cathode in acetonitrile to an 8,8'-dimer.³⁹⁶

e. *Derivatives of 1,2,4-Triazine.* The electrochemical reduction of 5,6-diphenyl-1,2,4-triazin-3-one (**255**) leads to a 1,4-dihydro derivative, which rearranges to a 4,5-dihydro compound. This is a cyclic semicarbazone and is accordingly reduced in acid solution with cleavage of the N—N bond to an imidazolone (**256**); in less acidic or alkaline solution, the 1,4,5,6-tetrahydro derivative is formed³⁹⁷ [Eq. (136)].

³⁹⁰ J. D. Porter, S. Fletcher, and R. G. Barradas, *J. Electrochem. Soc.* **126**, 1693 (1979).

³⁹¹ T. Troll and G. W. Ollmann, *Tetrahedron Lett.* **22**, 3497 (1981).

³⁹² T. Wasa and P. J. Elving, *J. Electroanal. Chem.* **91**, 249 (1978).

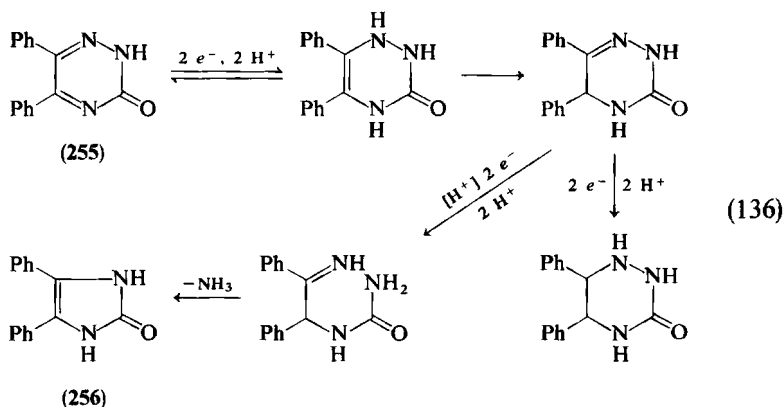
³⁹³ T. E. Cummings and P. J. Elving, *J. Electroanal. Chem.* **102**, 237 (1979).

³⁹⁴ T. E. Cummings and P. J. Elving, *J. Electroanal. Chem.* **94**, 123 (1978).

³⁹⁵ P. Pflögel and G. Wagner, *Pharmazie* **27**, 24 (1972).

³⁹⁶ E. Szebenyi-Gyori, K. Koleszar, V. Koracs-Mindler, I. Hermecz, G. Horvath, and G. Toth, *Magy. Kem. Foly.* **88**, 327 (1982) [*CA* **97**, 135650 (1982)].

³⁹⁷ J. Pinson, J.-P. M'Packo, N. Vinot, J. Armand, and P. Bassinet, *Can. J. Chem.* **50**, 1581 (1972).



Similar saturation of a C=N bond is found in the reduction (pH 4.5 or 9) of 3-methoxycarbonyl-5-methylfuro[2,3-*d*]pyridazin-4-one.³⁹⁸

f. Derivatives of Purine and Pteridine. The two-electron reduction of 7-methylguanosine in acid solution takes place in the imidazolinium ring to the 7,8-dihydro derivative with saturation of the C=N bond; the electrochemical reduction thus leads to the same product as the reduction with NaBH₄.³⁹⁹

6,7-Dioxotetrahydropteridines are reduced analogously⁴⁰⁰ to the 2,3-dioxoquinoxalines; a reduction scheme was proposed in Part I and substantiated later.⁴⁰¹ The primary two-electron reduction product is an enediol that isomerizes to a hydroxycarbonyl compound. After loss of water, the double bond is saturated with the uptake of two electrons and protons and a monooxytetrahydropyrazine ring is formed.

G. Dryhurst and co-workers have investigated the electrochemistry of naturally occurring *N*-heterocyclic molecules, including uric acid, xanthine, adenine, and guanine,^{5,402} in the expectation that the mechanisms observed electrochemically might lead to a more detailed understanding of the biological redox reactions of these molecules.

At a pyrolytic graphite anode, uric acid (257) undergoes a two-electron oxidation to an unstable diimine species (258), which is then hydrated in

³⁹⁸ A. Daver, *C. R. Acad. Sci., Ser. C* **274**, 244 (1972).

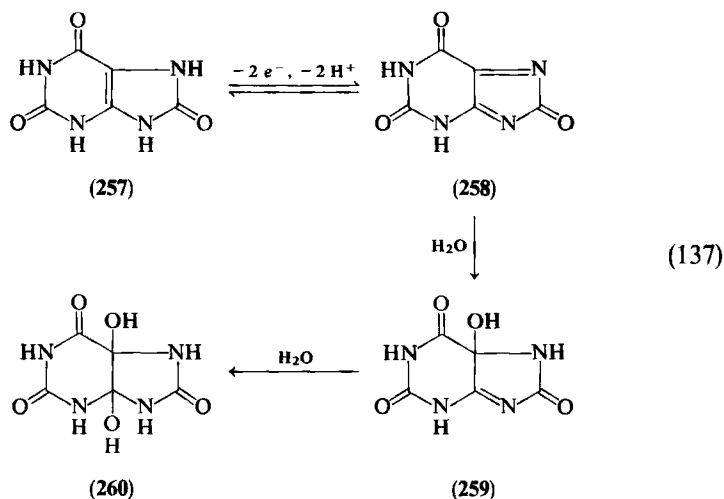
³⁹⁹ J. M. Sequaris and J. A. Reynaud, *J. Electroanal. Chem.* **63**, 207 (1975).

⁴⁰⁰ R. Gottlieb and W. Pfeleiderer, *Chem. Ber.* **111**, 1763 (1978).

⁴⁰¹ J. Armand, Y. Armand, and L. Boulares, *C. R. Acad. Sci., Ser. C* **286**, 17 (1978).

⁴⁰² G. Dryhurst, *Top. Curr. Chem.* **34**, 47 (1972).

two steps to give first an imino alcohol (**259**) and then the diol **260**. The latter compound decomposes to a number of products, the nature of which is controlled largely by the pH of the solution^{403,404} [Eq. (137)].



The electrochemical oxidation of several N-methylated uric acids,^{405,406} as well as application of thin-layer, spectroelectrochemical, and GLC-MS techniques,⁴⁰⁷ supported the sequence of the reaction steps shown in Eq. (137).

The electrochemical oxidation of hypoxanthine (**261**) in aqueous solution gave the intermediate 6,8-dioxopurine (**262**), which is more easily oxidized than **261**, leading to 6,8-dioxopurinediimine (**263**).⁴⁰⁸ It is proposed that the nucleophilic attack of water occurs at the 4- or 5-position of **263**, leading to the imino alcohols **264** or **265** [Eq. (138)]. These two compounds decompose by subsequent chemical or electrochemical reactions to the three major final products: 5-imino-2,4-imidazoledione, 5-hydroxyhydantoin-5-carboxamide, and 4-amino-4-carboxyimidazol-5-one.

⁴⁰³ G. Dryhurst, *J. Electrochem. Soc.* **119**, 1659 (1972).

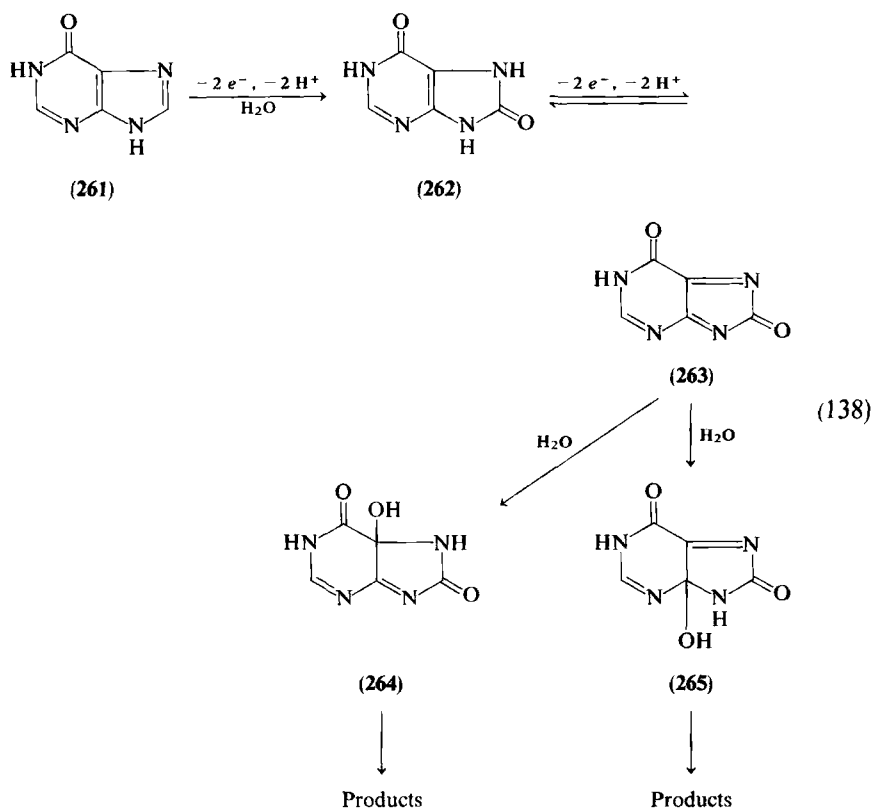
⁴⁰⁴ J. L. Owens, H. A. Marsh, and G. Dryhurst, *J. Electroanal. Chem.* **91**, 231 (1978).

⁴⁰⁵ M. Z. Wrona, J. L. Owens, and G. Dryhurst, *J. Electroanal. Chem.* **105**, 295 (1979).

⁴⁰⁶ M. T. Cleary, J. L. Owens, and G. Dryhurst, *J. Electroanal. Chem.* **123**, 265 (1981).

⁴⁰⁷ A. Brajter-Toth and G. Dryhurst, *J. Electroanal. Chem.* **122**, 205 (1981).

⁴⁰⁸ A. C. Conway, R. N. Goyal, and G. Dryhurst, *J. Electroanal. Chem.* **123**, 243 (1981).

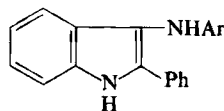
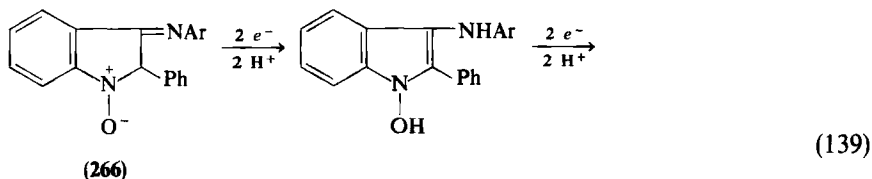


Anodic oxidation of 6- and 7-pteridone, using electrolysis at a controlled potential, gave pteridine-6,7-dione in 95–100% yield.⁴⁰⁹ Under controlled-potential electrolysis conditions pteridine-6,7-dione is oxidized to the bridge-head diol, which undergoes rearrangement, further oxidation, and hydrolysis, yielding tetraketopiperazine, oxamide, urea, oxamic acid, ammonia, formaldehyde, formic acid, and CO₂.

g. *N*-Oxides and *S*-Oxides. In Part I the reactions of a number of mono- and di-*N*-oxides and *S*-oxides were discussed. Here only a few will be mentioned.

⁴⁰⁹ D. L. McAllister and G. Dryhurst, *J. Electroanal. Chem.* **55**, 69 (1974).

2-Phenyl-3-aryliminoindolenine 1-oxides (**266**) are reduced⁴¹⁰ in DMF containing a strong proton donor in two two-electron reductions, according to Eq. (139).



1,1'-Dioxy-2,2'-diphenyl- $\Delta^{3,3'}$ -bi-3*H*-indole is reduced under similar conditions in an analogous way.⁴¹¹

C. ALDEHYDES AND KETONES

The fundamental electrode reactions of aldehydes and ketones were discussed in Part I.

The three acetylpyridines have been reduced in the presence of catalytic concentrations of different alkaloids in attempts to induce optical activity in the products.⁴¹² The reduction of 3-acetylpyridine gave optically inactive alcohols under all conditions employed, whereas optically active pyridyl-ethanols are produced from 2- and 4-acetylpyridine at 0°C, in a 1:1 aqueous-ethanolic acetate buffer with strychnine (5×10^{-4} M) as chiral catalyst. Under these conditions protonated, adsorbed strychnine is probably acting as a chiral acid. The pinacols obtained as side products were all optically inactive.

D. CARBOXYLIC ACIDS AND DERIVATIVES

Kolbe reactions of *N*-heterocyclic compounds have been studied in only a few cases. It appears that the oxidative decarboxylation involves the removal of electrons through the heterocyclic π -system and is of the "pseudo

⁴¹⁰ R. Andruzzi, M. E. Cardinali, and A. Trazza, *J. Electroanal. Chem.* **41**, 67 (1973).

⁴¹¹ R. Andruzzi, A. Trazza, and P. Bruni, *J. Electroanal. Chem.* **51**, 341 (1974).

⁴¹² J. Kopilov, E. Kariv, and L. L. Miller, *J. Am. Chem. Soc.* **99**, 3450 (1977).

Kolbe" type.⁴¹³ The reaction could take place by two paths: by electron removal from the π system in a conventional ECE process to give an O- π -stabilized radical or by a concerted two-electron removal from the heterocyclic π system, and CO₂ loss.

Anodic oxidation of 1,3-diaryl-5-methyl- Δ^2 -pyrazoline-5-carboxylic acids in CH₃CN-Et₄NBF₄ proceeded with decarboxylation to the aromatized pyrazoles in high yield.⁴¹⁴ Similarly, electrochemical oxidation of *N*-acetyl-2,3-substituted Δ^4 -pyrroline-2-carboxylic acids in water-tetrahydrofuran (3:1) containing KOH forms the corresponding pyrroles (80–98%).⁴¹⁵

Anodic oxidation of dihydroorotic acid, its isomer, and the 1-benzyl analog of dihydroorotic acid in H₂O-NaOH media is an efficient synthesis of uracils (51–91%) under mild conditions.⁴¹⁶

1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acids have been anodically decarboxylated in MeOH-NaOMe on a graphite felt anode, giving 3,4-dihydroisoquinolines (50–90%).⁴¹⁷ This may be an example of a pseudo-Kolbe reaction in support of Hahn's theory of the biosynthesis of isoquinoline alkaloids by providing a laboratory analogy for the crucial decarboxylation step.

Nitriles

The reduction of 2- and 4-cyanopyridine to the aminomethylpyridine was mentioned in Part I. 3-Aminomethylpyridine has been prepared from 3-cyanopyridine in an electrocatalytic reduction in aqueous hydrochloric acid solution, using an electrode consisting of a thinly deposited layer of palladium black on graphite. The reduction proceeds with electrolytically generated hydrogen not via an electron transfer to the substrate.⁴¹⁸

E. NITROGEN-CONTAINING SUBSTITUENTS

Amino Groups

An amino group usually merely modifies the conditions for reduction of the heterocyclic nucleus, but the amino group is reductively lost in some cases, e.g., in 4-aminoquinazoline⁴¹⁹ [Eq. (140)].

⁴¹³ J. P. Coleman and L. Eberson, *J. C. S. Chem. Commun.*, 1300 (1971).

⁴¹⁴ A. Diaz, *J. Org. Chem.* **42**, 3949 (1977).

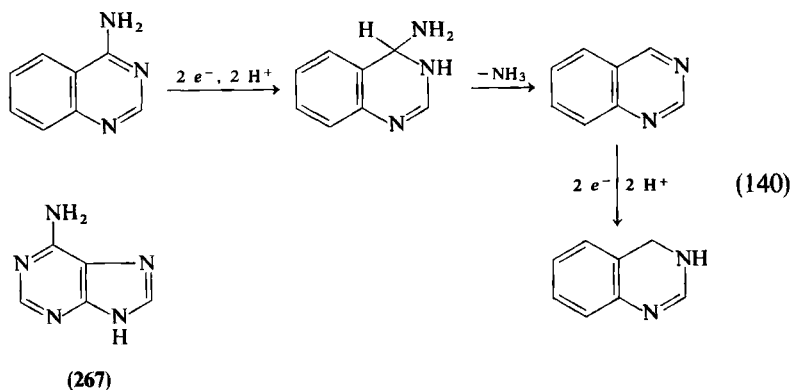
⁴¹⁵ H. Horikawa, T. Iwasaki, K. Matsumoto, and M. Miyoshi, *J. Org. Chem.* **43**, 335 (1977).

⁴¹⁶ K. Matsumoto, H. Horikawa, T. Iwasaki, and M. Miyoshi, *Chem. Ind. (London)*, 920 (1978).

⁴¹⁷ J. M. Bobbitt and T. Y. Cheng, *J. Org. Chem.* **41**, 443 (1976).

⁴¹⁸ V. Krishnan, K. Raghupathy, and H. V. K. Udupa, *J. Electroanal. Chem.* **88**, 433 (1978).

⁴¹⁹ S. Kwee and H. Lund, *Acta Chem. Scand.* **25**, 1813 (1971).



The reduction of adenine (267) is suggested to follow⁴²⁰ a similar route rather than that described in Part I, and that purine is formed after the first two-electron reduction and elimination of ammonia. A similar route is possibly followed in the deamination of 7-amino-6-phenylpyrazolo[1,5-*a*]-pyrimidine.³⁵¹ Reduction followed by elimination is probably the most general reaction path for removing substituents bound to a heterocyclic ring through O, N, or S.

The electrochemical oxidation of 4-dimethylaminoantipyrene (4-dimethyl-amino-2,3-dimethyl-1-phenyl- Δ^3 -pyrazolin-5-one) has been investigated in $\text{CH}_3\text{CN}-\text{NaClO}_4$ at a glassy carbon electrode.⁴²¹ The first step is a quasi-reversible electron transfer from the lone-pair electrons on the 4-dimethyl-amino nitrogen to form the radical-cation. The second-order disappearance of the radical-cation is presumably due to a disproportionation reaction. The oxidation at the potential of the plateau of the first wave gave the protonated 4-dimethylaminoantipyrene in $\sim 60\%$ yield, but other products were not identified.

Electrochemical oxidation of 2-, 3-, and 4-aminopyridines as well as 2,6-diaminopyridines and aminopicolines was studied in $\text{CH}_3\text{CN}-\text{LiClO}_4$ by means of RDE voltammetry.⁴²² Also, the electrochemical oxidation of 3-aminopyridine, 2,3-diaminopyridine, and 2,6-diaminopyridine has been investigated in aqueous solutions in the pH range 0.7–13 at platinum and carbon paste solid electrodes.⁴²³ A reaction scheme for the oxidation of aminopyridines was proposed on the basis of the voltammetric results, but the products of the oxidations were not identified.

⁴²⁰ S. Kwee and H. Lund, *Acta Chem. Scand.* **26**, 1195 (1972).

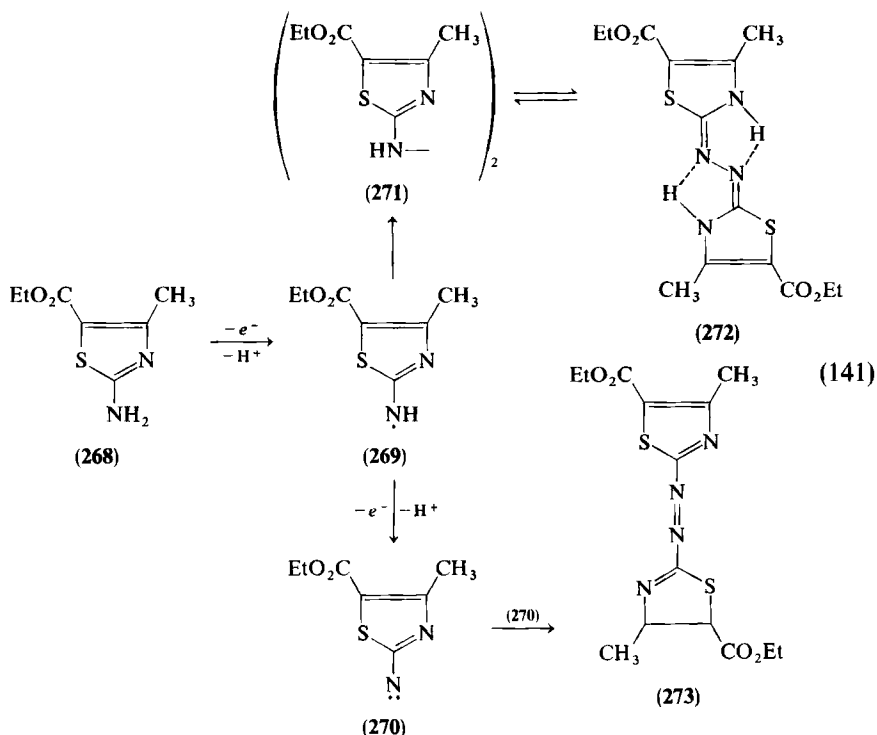
⁴²¹ H. Sayo and M. Masui, *J. C. S. Perkin II*, 1640 (1973).

⁴²² I. B. Romanova and L. V. Chervina, *Khim. Geterotsikl. Soedin.*, 1654 (1977) [*CA* **88**, 96630 (1978)].

⁴²³ P. G. Desideri, D. Heimler, and L. Lepri, *J. Electroanal. Chem.* **88**, 407 (1978).

The oxidation of 2-phenyl-3-arylaminoindoles has been studied in CH_3CN , DMF, and propylene carbonate at a platinum electrode with periodic renewal of the diffusion layer. The oxidation proceeds in two one-electron steps, the first leading to the formation of a radical-cation, which in the second step is oxidized at a more positive potential.⁴²⁴ The main concentration of charge and unpaired spin in the radical-cation are at the amino group. In the presence of base, 2-phenyl-3-arylaminoindoles undergo a two-electron oxidation to the corresponding imines.

The anodic oxidation of 2-amino-5-ethoxycarbonyl-4-methylthiazole (**268**) has been studied in $\text{CH}_3\text{CN}-\text{LiClO}_4$.⁴²⁵ The mechanism of the formation of azo (**273**) and hydrazo (**271**) dimeric compounds as the main oxidation products is shown in Eq. (141).



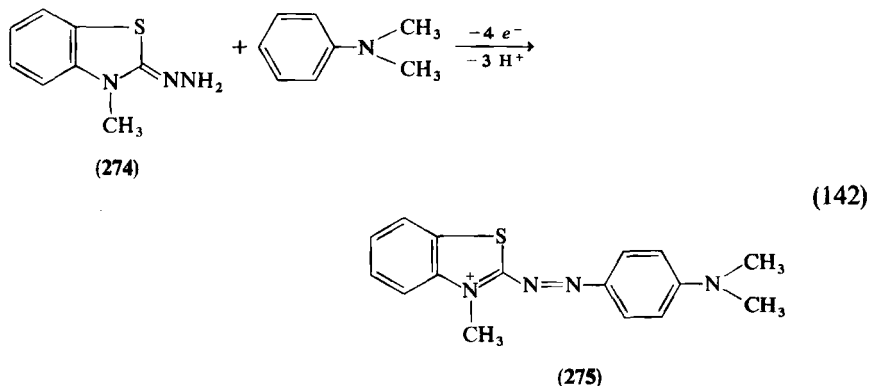
The compound **271** or **272** is obtained by dimerization of two radicals (**269**). It seems that stabilization of the hydrazo derivative through hydrogen bonding deactivates the molecule toward further oxidation. On the other

⁴²⁴ R. Andruzzi and A. Trazza, *J. Electroanal. Chem.* **86**, 201 (1978).

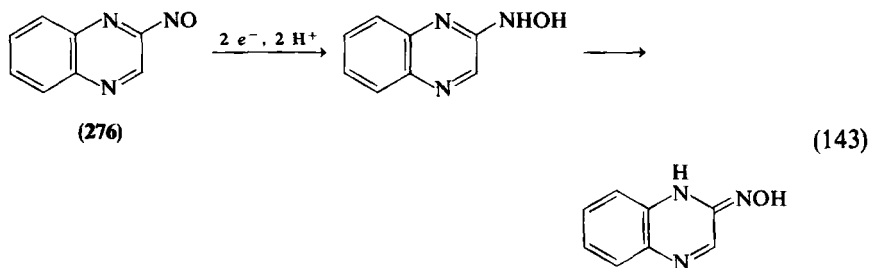
⁴²⁵ G. Cauquis, H. M. Fahmy, G. Pierre, and M. H. Elnagdi, *J. Heterocycl. Chem.* **16**, 413 (1979).

hand, the radical **269** may be further oxidized to the nitrene **270**, which then undergoes dimerization to afford **273**.

Another anodic coupling reaction was achieved by anodic oxidation of *N*-methylbenzthiazolone-2-hydrazone (**274**) in aqueous sulfuric acid containing dimethylaniline. The final product (**275**) was isolated in 30% yield⁴²⁶ [Eq. (142)].



The reduction of *N*-nitroso derivatives was discussed in Part I; *C*-nitroso compounds are generally reduced to the hydroxylamine, which in alkaline solution may react with the nitroso compound to form an azoxy compound, possibly through an electron transfer from the hydroxylamine to the nitroso compound. Nitrosoquinoxaline (**276**) behaves as an α,β -unsaturated nitroso compound; on reduction the primarily formed hydroxylamine tautomerizes to an oxime⁴²⁷ [Eq. (143)].

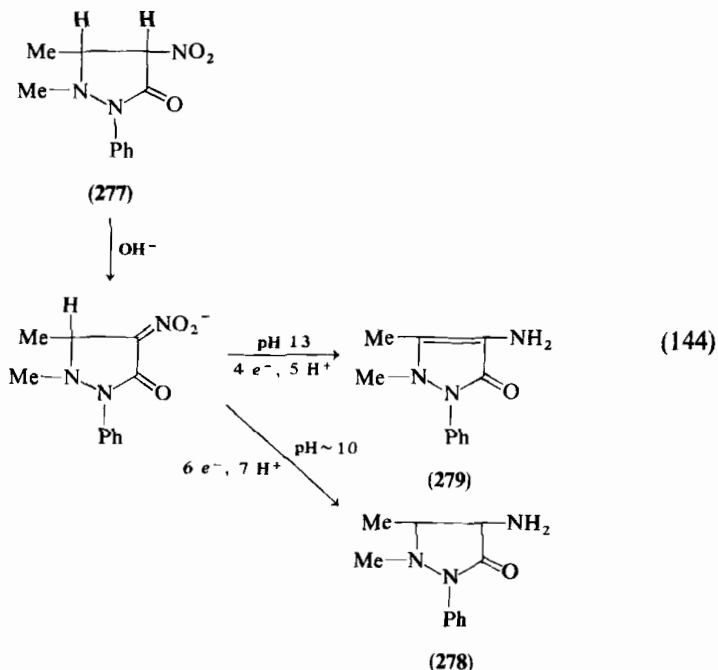


Nitro derivatives of heterocyclic compounds are generally reduced similarly to carbocyclic analogs. However, whereas nontertiary aliphatic or ali-

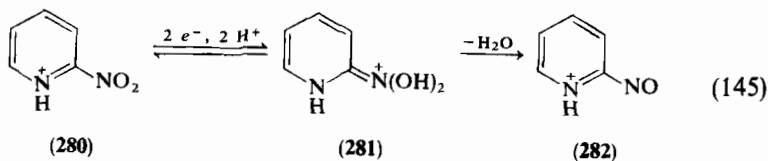
⁴²⁶ G. Henze and K. Keller, *Z. Chem.* **14**, 238 (1974).

⁴²⁷ J. Armand, Y. Armand, L. Boulares, M. Philoche-Levisalles, and J. Pinson, *Can. J. Chem.* **59**, 1711 (1981).

cyclic nitro compounds are not reducible in alkaline solution because of the formation of the nitronate anion, 2,3-dimethyl-4-nitro-1-phenylpyrazolidine-5-one (277) is reducible as the nitronate anion because of the neighboring carbonyl group. In weak alkali, 4-amino-2,3-dimethyl-1-phenylpyrazolidine-5-one (278) is formed in a six-electron reduction, whereas 4-aminoantipyrine (279) is the product at pH 13 formed in a four-electron reduction⁴²⁸ [Eq. (144)].



A reversible reduction of nitropyridines,^{429,430} e.g., **280** in acidic, aqueous ethanol at -7°C leads [Eq. (145)] to the corresponding dihydroxylamine (281), which produces the corresponding nitrosopyridine (282) by elimination



⁴²⁸ D. M. Hamel and H. Oelschläger, *J. Electroanal. Chem.* **28**, 197 (1970).

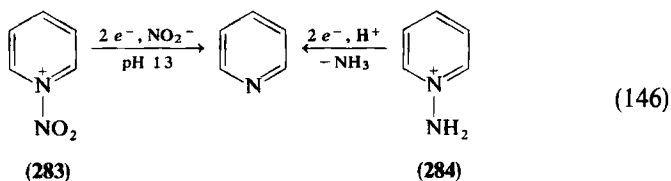
⁴²⁹ A. Darchen and C. Moinet, *J. C. S. Chem. Commun.*, 487 (1976).

⁴³⁰ A. Darchen and C. Moinet, *J. Electroanal. Chem.* **68**, 173 (1976).

of water. Compound **282** is more easily reduced than **280**. It is, in a way, analogous to the reduction of pyridine carboxylic acid derivatives to *gem*-diols, which are dehydrated to the more easily reducible aldehydes (Part I). Nitro derivatives of other π -electron-deficient heterocycles are expected to behave similarly.

N-Nitraminopyridines are reducible both in acid and alkali. In hydrochloric acid the main product from 2-nitraminopyridine was the hydrazinopyridine, formed in a six-electron reduction, but 2-aminopyridine and 2-chloropyridine were side products, the latter possibly through reaction by an intermediate diazonium compound with chloride. Contrary to nitramines of most primary amines, 2-nitraminopyridine⁴³¹ is reducible in alkaline solution; uptake of the first two electrons forms the 2-pyridyl-*N*-nitrosamine, which is further reduced to 2-aminopyridine.

Pyridine-1-nitroimide (**283**) in both acid and alkali is reduced to pyridine in a two-electron reduction; in acid, 1-aminopyridinium ion (**284**) is also reduced to pyridine⁴³¹ [Eq. (146)].



F. SULFUR-CONTAINING SUBSTITUENTS

The reduction and reductive elimination of sulfur-containing substituents was treated in Part I.

Anodic oxidation of heterocyclic thiones leads generally to disulfides. Thus cyclic voltammetric data at a pyrolytic graphite anode of purine-2,6-dithione show three peaks. The first and second correspond to a disulfide formation from the 6- and 2-thione groups, respectively, whereas the third is due to an oxidation to purine-2,6-disulfonic acid.⁴³² Similarly, the electrochemical oxidation of benzthiazole-2-thione and benzimidazole-2-thione in CH_3CN - NaClO_4 at a platinum electrode afforded the corresponding disulfides in good yield.⁴³³

⁴³¹ H. Lund and S. K. Sharma, *Acta Chem. Scand.* **26**, 2324 (1972).

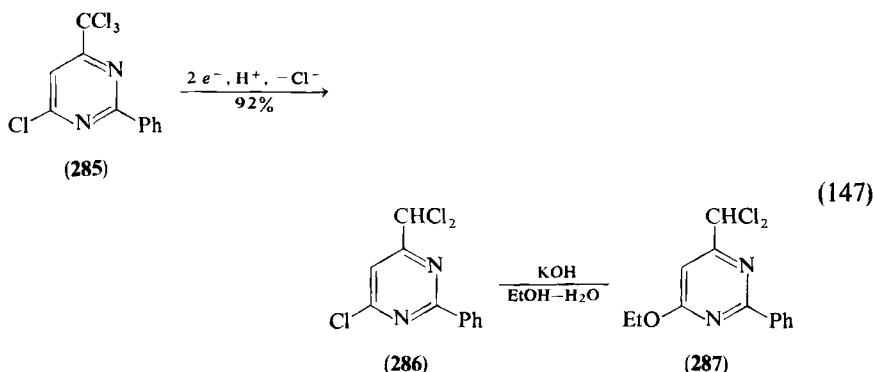
⁴³² G. Dryhurst, *J. Electrochem. Soc.* **117**, 1113 (1970).

⁴³³ H. Berge, H. Millat, and B. Strübing, *Z. Chem.* **15**, 37 (1975).

G. HALOGEN DERIVATIVES

1. Halogenated Side Chains

Stepwise reductive removal of halogen may have synthetic value, e.g., the reduction of a trichloromethyl group to a dichloromethyl group, which might be hydrolyzed to an aldehyde group. Reduction of 6-chloro-2-phenyl-4-trichloromethylpyrimidine (**285**) in DMF¹⁷³ containing 0.5% acetic acid and a little water gave 92% of 6-chloro-2-phenyl-4-dichloromethylpyrimidine (**286**). This dichloromethyl group is resistant to hydrolysis; refluxing for 12 h with 0.2 M KOH in a 3:2 mixture of water and ethanol gave 6-ethoxy-2-phenyl-4-dichloromethylpyrimidine (**287**) [Eq. (147)].



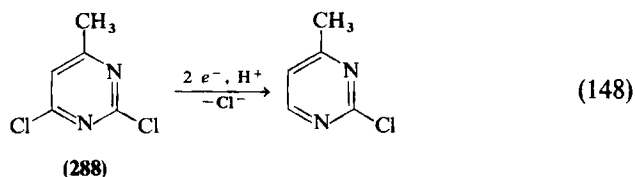
2. Halogenated Nuclei

Aromatic and heteroaromatic halogen compounds⁴³⁴ are reduced in aprotic media to a radical-ion, which more or less rapidly may lose a halide ion. Iodo compounds are cleaved faster than the corresponding chloro derivatives, and bromo compounds are cleaved at intermediate rates. The reduction potential plays⁴³⁵ a role in the rate of cleavage; generally, the more negative the reduction potential, the faster a given C-halogen bond is cleaved. The rate of the cleavage may be found by suitable electroanalytic methods (Section II,A); in that section an example of the synthetic use of the knowledge of the rate constants of competing follow-up reactions was given.

⁴³⁴ M. D. Hawley, in "Encyclopedia of Electrochemistry of the Elements" (A. J. Bard and H. Lund, eds), Vol. 14, Chapter 4. Dekker, New York, 1980.

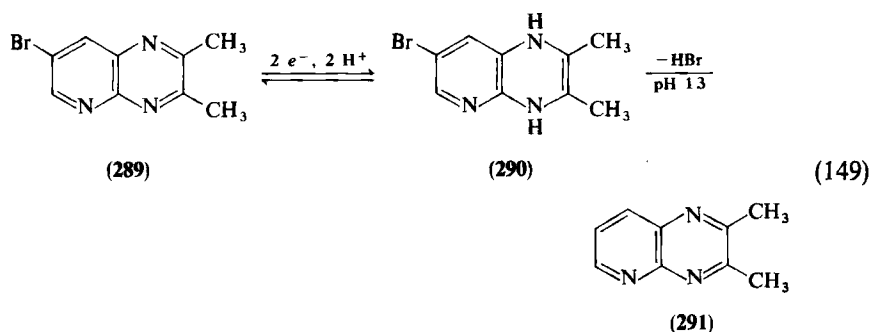
⁴³⁵ K. Alwair and J. Grimshaw, *J. C. S. Perkin II*, 1811 (1973).

A number of preparatively useful reductions with removal of halogen was discussed in Part I. Often a stepwise removal of the halogens takes place in a polyhalogenated compound. 4-Methyl-2,6-dichloropyrimidine (**288**) thus gives three peaks in DMF, the third peak being the reduction of the nucleus. Preparative reduction at the potential of the first peak affords 4-methyl-2-chloropyrimidine⁴³⁶ [Eq. (148)].



The more nitrogen the heteroaromatic nucleus contains, the more easily reducible it is; in such cases the nucleus may be reduced in preference to a carbon-halogen bond. Thus whereas the first reduction of 2-(diethyl-amino)-4,6-dichloro-*s*-triazine in aqueous solution is a reductive removal of a chlorine, the second reduction is of the nucleus.^{437,438}

In acidic solution, 7-bromo-2,3-dimethylpyrido[2,3-*b*] pyrazine (**289**) is reduced reversibly to the 1,4-dihydro derivative **290** without loss of bromide, whereas in alkaline solution the primarily formed dihydro compound loses hydrogen bromide to the parent pyrido[2,3-*b*]pyrazine (**291**), which may be further reduced³⁵⁰ [Eq. (149)].



2,3,5-Tribromothiophene is reduced in good current yield to 3-bromothiophene in 70% dioxane-30% water with sodium bromide as supporting electrolyte. At the anode the generated bromine may be used for bromination of thiophene.⁴³⁹

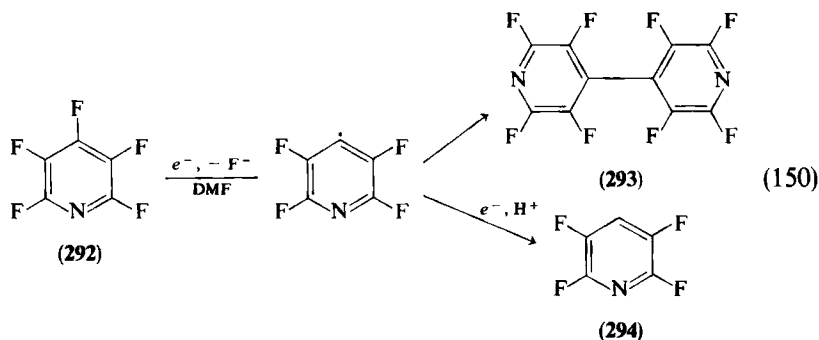
⁴³⁶ H. Lund, unpublished observation.

⁴³⁷ E. Yu. Khmel'nitshaya, *Elektrokhimiya* **10**, 165 (1974) [*CA* **80**, 81748 (1974)].

⁴³⁸ E. Yu. Khmel'nitskaya, *Elektrokhimiya* **11**, 873 (1975) [*CA* **83**, 154656 (1975)].

⁴³⁹ D. Pletcher and M. Razaq, *J. Appl. Electrochem.* **10**, 575 (1980).

Pentafluoropyridine (**292**) is reduced⁴⁴⁰ in dry DMF at a mercury cathode to perfluoro-4,4'-bipyridyl (**293**); in the presence of hydroquinone as proton donor, 2,3,5,6-tetrafluoropyridine (**294**) is obtained [Eq. (150)]. Pentachloropyridine gives on reduction in dry DMF very little bipyridyl derivative, but tetrachloropyridine and bis(tetrachloropyridyl) mercury.



In THF-H₂O (1:1), pentachloropyridine is reduced at a silver cathode to 2,3,5,6-tetrachloropyridine and further to 2,3,5-trichloropyridine. 3,4,5,6-Tetrachloro-2-picolinic acid may similarly be stepwise reduced.^{441,442}

⁴⁴⁰ R. D. Chambers, W. K. R. Musgrave, C. R. Sargent, and F. G. Drakesmith, *Tetrahedron* 37, 591 (1981).

⁴⁴¹ D. Kyriacou, European Patent Appl. 18,069 (1980); [CA 94, 54933 (1981)].

⁴⁴² F. Y. Edamura, D. Kyriacou, and J. Love, U.S. Patent 4,217,185 (1980) [CA 94, 22193 (1981)].

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The Chemistry of Pyrazolopyridines

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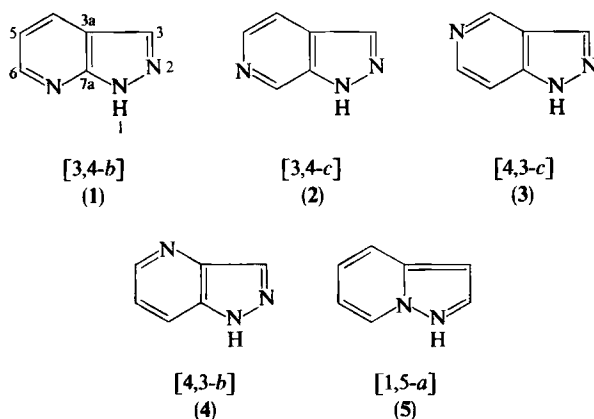
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I. Introduction

The pyrazolopyridines comprise five isomers (1–5), derivatives of which were first reported in 1906,¹ 1934,² 1906,³ 1958,⁴ and 1957,⁵ respectively. Pyrazolopyridines have continued to attract interest because of their biological activity and structural relationship to indoles⁶ and azaindoles (pyrrolopyridines).⁷ Pratap⁸ published a brief outline of synthetic routes to derivatives of 1 and 3 but the subject has not been comprehensively reviewed.



The system of nomenclature is that of *Chemical Abstracts*. Alternative systems based on diazaindenes or triazaindoles have, however, appeared in early papers; pyrazolo[1,5-*a*]pyridines are occasionally reported as pyrazolo[2,3-*a*]pyridines or 3-azaindolizines.

¹ G. Ortoleva, *Gazz. Chim. Ital.* **36**, 473 (1906).

² S. M. E. Englert and S. M. McElvain, *J. Am. Chem. Soc.* **56**, 700 (1932).

³ A. Michaelis, *Justus Liebigs Ann. Chem.* **366**, 324 (1906).

⁴ I. L. Finar and R. J. Hurlock, *J. Chem. Soc.*, 3259 (1958).

⁵ J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 4506 (1957).

⁶ B. Robison, *Chem. Rev.* **69**, 227 (1969).

⁷ R. E. Willele, *Adv. Heterocycl. Chem.* **2**, 27 (1968).

⁸ R. R. Pratap, *Rec. Chem. Prog.* **29**, 103 (1968).

Compounds containing a potential hydroxy group (Section IV,3,b) are drawn in the lactam form. References to hydroxy derivatives in the text are used for convenience and are not intended to implicate a particular tautomer.

This review covers the literature to June, 1982; no attempt is made to discuss biological activity.

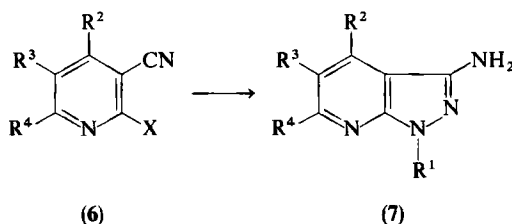
II. Methods of Synthesis

A. SYNTHESIS OF PYRAZOLO[3,4-*b*]PYRIDINES

Pyrazolo[3,4-*b*]pyridines have received considerable attention as a result of their biological activity. Although much of the early literature on their synthesis is confused, due to erroneous structural assignments, this has been resolved in many cases by the use of spectroscopic techniques.

1. From 2-Chloro-3-cyanopyridines

Condensation of 2-chloro-3-cyanopyridines **6** ($X = \text{Cl}$) with hydrazines yields 3-aminopyrazolo[3,4-*b*]pyridines **7**. The majority of workers⁹⁻¹⁵ report 1-*H* derivatives but 1-substituted compounds have also been prepared.^{9,16,17} In one instance⁹ a hydrazinopyridine (**6**: $R^2 = \text{H}$, $R^3 = \text{CN}$,



⁹ S. G. Cottis, P. B. Clarke, and H. Tieckelmann, *J. Heterocycl. Chem.* **2**, 192 (1965).

¹⁰ T. L. P. Hatt and J. D. R. Vass, *J. C. S. Chem. Commun.*, 293 (1966).

¹¹ M. Lacen and K. Tabakovic, *Croat. Chim. Acta* **47**, 127 (1975).

¹² J. Roch, E. Mueller, B. Narr, J. Nickl, and W. Haarmann, Ger. Offen. 2,643,753 (1978) [*CA.* **89**, 6322 (1978)].

¹³ G. Y. Leshner and M. D. Gruett, U.S. Patent 4,264,603 (1980) [*CA.* **95**, 62198 (1981)].

¹⁴ J. Roch, E. Mueller, B. Narr, J. Nickl, and W. Haarmann, U.S. Patent 4,260,621 (1981) [*CA.* **95**, 20953 (1981)].

¹⁵ R. Balicki and P. Nantka-Namirski, *Pol. J. Chem.* **53**, 1515 (1979).

¹⁶ E. Fleckenstein and R. Mohr, Ger. Offen. 2,232,038 (1974) [*CA.* **81**, 93080 (1974)].

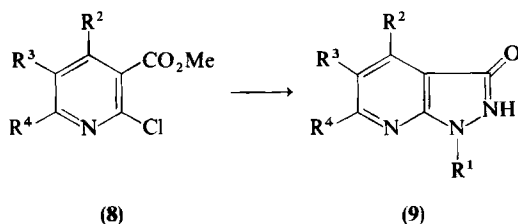
¹⁷ L. Kuczynski, A. Mrozikiewicz, W. Banoskiewicz, and K. Poreba, *Pol. J. Pharmacol. Pharm.* **31**, 217 (1979).

$R^4 = NH_2$, $X = NHNH_2$) was obtained, which cyclized in boiling hydrochloric acid or dimethyl formamide. The corresponding intermediate from methylhydrazine, however, could not be isolated.⁹

In addition, amines **7** ($R^1 = H$) have been produced from other 2-substituted 3-cyanopyridines (**6**: $X = SO_3H$, SMe) in good or moderate yield.¹⁸

2. From 2-Chloronicotinic Acid Derivatives

The reaction of hydrazines with 2-chloronicotinic acid derivatives affords pyrazolones **9** either directly or via the isolated hydrazines or hydrazides.



For example, treatment of esters **8**¹⁹⁻²¹ with hydrazine in refluxing ethanol gave the N-unsubstituted bicycles **9** ($R^1 = H$). 1-Methyl derivatives (**9**: $R^1 = Me$) were also prepared.²² The hydrazine **11**, obtained from the acid **10a**, was heated at reflux without purification in dilute acid to give **12** ($R = H$). The acid chloride **10b** furnished hydrazide intermediates **10c**,^{17,23,24} which were cyclized by fusing the solid,²³ refluxing with pyridine in the presence of copper powder,²⁴ or by heating with potassium carbonate in 1-pentanol.¹⁷

Condensation of unsymmetrical hydrazines with 2-chloronicotinic acid derivatives has generally yielded 1-substituted products, but the acid chloride **10a** and benzylhydrazine afforded, via the hydrazide **10d**, 2-benzyl compound **13**.²³ The isomer **12** ($R = CH_2Ph$) was obtained either directly from the ester **10e** or from **14** via the hydrazide **10c**.²³

¹⁸ U. Schmidt and G. Giesselmann, *Chem. Ber.* **93**, 1590 (1960).

¹⁹ I. Sekikawa, J. Nishie, S. Tonooka, Y. Tanaka, and S. Kakimoto, *J. Heterocycl. Chem.* **10**, 931 (1973).

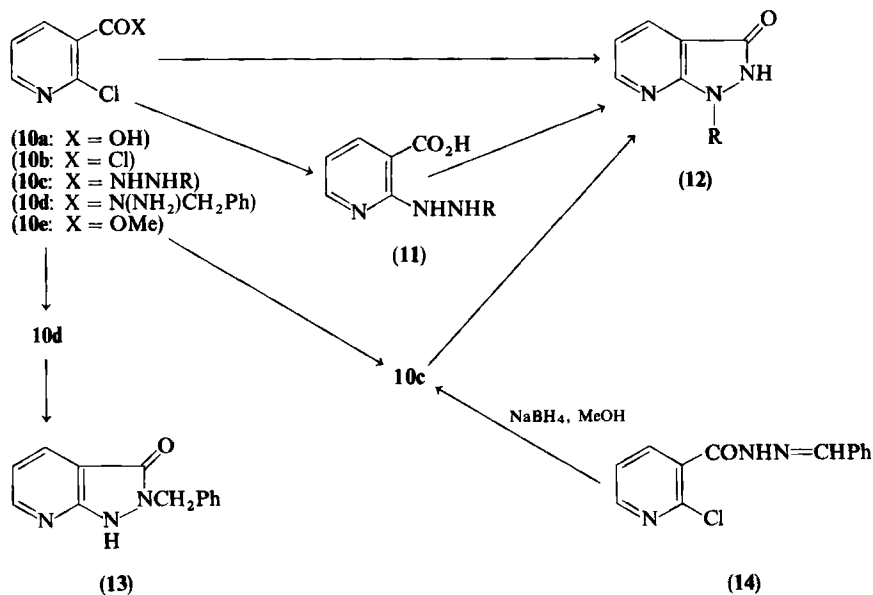
²⁰ R. Balicki, L. Kaczmarek, and P. Nantka-Namirski, *Acta Pol. Pharm.* **33**, 289 (1976).

²¹ P. Schmidt, K. Eichenberger, and M. Wilhelm, *Angew. Chem.* **73**, 15 (1961).

²² G. Y. Leshner and M. D. Gruett, U.S. Patent 4,265,895 (1981) [*C.A.* **95**, 62200 (1981)].

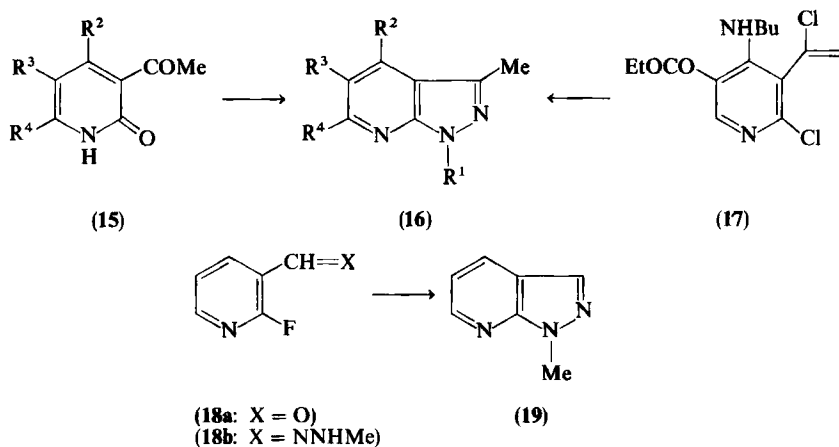
²³ L. Baiocchi, *Ann. Chim. (Rome)* **60**, 403 (1970).

²⁴ P. Bellani, E. Lauria, and G. Zoni, *Farmaco, Ed. Sci.* **26**, 872 (1971).



3. From 3-Acetylpyridines

The 3-acetylpyridines **15** condensed with hydrazines to afford 1-substituted derivatives (**16**: R¹ = H, Ph, CONH₂),²⁵ which may also be prepared²⁶ from the chlorovinylpyridine **17**.



²⁵ M. Abdalla, A. Essawy, and A. Deeb, *Indian J. Chem., Sect. B* **16B**, 332 (1978).

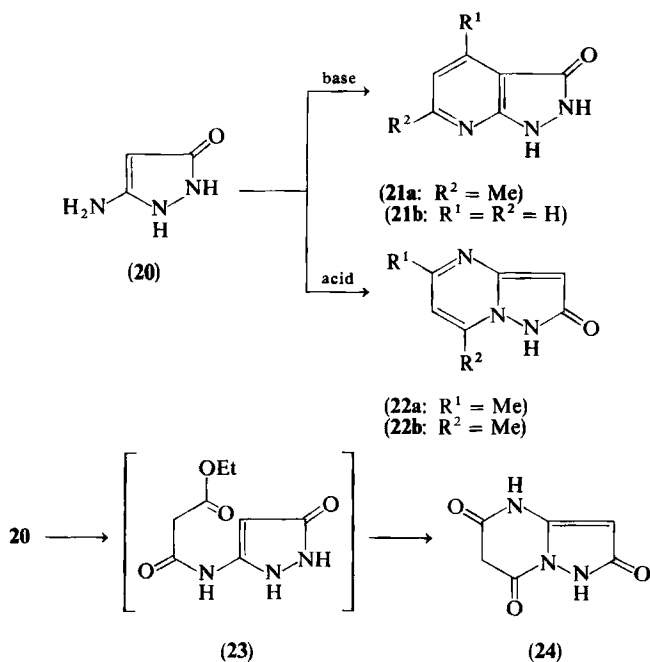
²⁶ T. Denzel, *Arch. Pharm. (Weinheim, Ger.)* **307**, 177 (1974).

2-Fluoropyridine-3-carboxaldehyde (**18a**), however, under similar conditions gave the hydrazone **18b**, which on treatment with base afforded **19**.²⁷

4. From 1-H-3-Amino-5-pyrazolones

The reaction of 1,3-dicarbonyl compounds with 3-amino-5-pyrazolones has been used extensively in the preparation of pyrazolo[3,4-*b*]pyridines. A number of products are possible, depending on the reagent used and the direction of cyclization. As a consequence, many of the early reports proposed incorrect structures.

a. *Reaction with Symmetrical 1,3-Dicarbonyl Compounds.* Cyclization of 3-amino-5-pyrazolone (**20**) gives pyrazolo[3,4-*b*]pyridines and/or the isomeric pyrazolo[1,5-*a*]pyrimidines, which are distinguishable by ¹H-NMR spectrometry. For example, **20** and acetylacetone under basic conditions^{21,28-31} give a product identified²⁸ as **21a** ($R^1 = \text{Me}$) whereas, in the



²⁷ D. Bonnetaud, G. Queguiner, and P. Pastour, *J. Heterocycl. Chem.* **9**, 165 (1972).

²⁸ J. L. Imbach, R. Jacquier, and J. L. Vidal, *Bull. Soc. Chim. Fr.*, 1929 (1970).

²⁹ P. Schmidt, K. Meier, and J. Druey, *Angew. Chem.* **70**, 344 (1958).

³⁰ E. C. Taylor and J. W. Barton, *J. Am. Chem. Soc.* **81**, 2448 (1959).

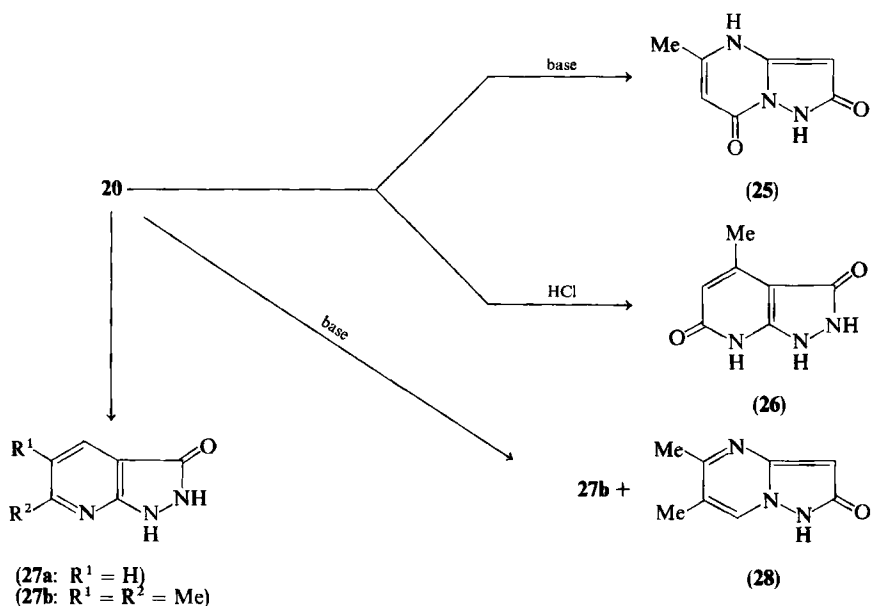
³¹ W. Reid and E. U. Kocher, *Justus Liebigs Ann. Chem.* **647**, 116 (1961).

presence of hydrochloric^{29,31} or glacial acetic acids,²⁸ the isomeric pyrimidine **22a** ($R^2 = \text{Me}$) was formed. In contrast, cyclization with malondialdehyde diacetal afforded the pyridine **21b**.²⁸

Later,³² a monofluoromethyldione and **20** in refluxing glacial acetic acid afforded a mixture of three isomers (**21a** and **22b**; $R^1 = \text{CF}_3$; **22a**: $R^2 = \text{CF}_3$).

Imbach *et al.*²⁸ reinvestigated the condensation³³ of **20** with diethyl malonate and obtained **24** under a variety of conditions. The formation of an intermediate amide (**23**) was proposed.

b. Reaction with Unsymmetrical 1,3-Dicarbonyl Compounds. In contrast with results found using acetylacetone, treatment of **20** with ethyl acetoacetate in hydrochloric acid resulted in formation of pyrazolo[3,4-*b*]-pyridine **26**. Furthermore, the use of glacial acetic acid gave a mixture of products **25** and **26**.²⁸ Analogous results were obtained using ethyl 2-methylacetoacetate²⁸ and ethyl benzoylacetate.^{34,35} However, a number of



³² R. Balicki and P. Nantka-Namirski, *Pol. J. Chem.* **54**, 2175 (1980).

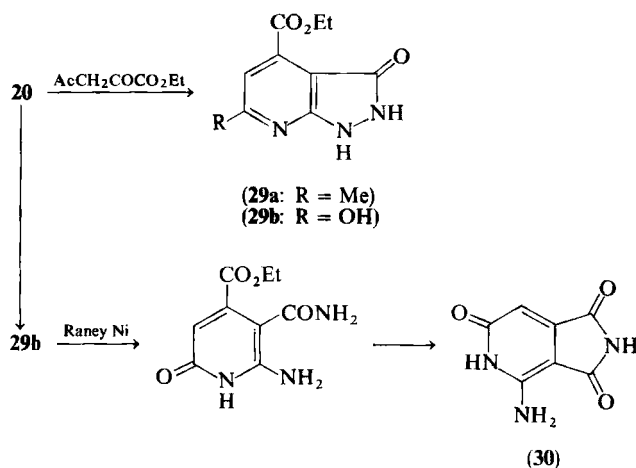
³³ A. Dornow and M. Siebrecht, *Chem. Ber.* **93**, 1106 (1960).

³⁴ R. Balicki, L. Kaczmarek, and P. Nantka-Namirski, *Pol. J. Chem.* **53**, 2491 (1979).

³⁵ P. Nantka-Namirski, R. Balicki, and M. Mordarski, Polish Patent 101,092 (1979) [*CA.* **93**, 95267 (1980)].

acylacetaldehydes reacted with **20** under basic conditions to afford 6-substituted pyrazolo[3,4-*b*]pyridines (**27a**: $R^2 = \text{Me, Ph, pyridyl}$).^{20,33,36} In addition, 2-acetylpropanal gave **27b** and the pyrimidine **28**.³³

Italian workers have investigated the reaction of **20** with keto acids. Ethyl 2,4-dioxovalerate condensed with **20** at 120°C to give a pyrazolopyridine (**29a**).³⁷ At higher temperatures a pyrazolo[1,5-*a*]pyrimidine isomer was formed as a by-product.³⁸ A similar reaction utilizing diethyl oxosuccinate gave the supposed 4-oxo isomer,³⁷ which was reassigned the 6-oxo structure **29b** on the basis of its conversion to the succinimide **30**.³⁸ The 6-oxo structure would seem more likely in view of analogous reactions³⁹ of 5-aminopyrazoles (Section II,A,6).



c. *Reaction with Methylaminovinyl Ketones or Aldehydes.* Under basic conditions a pyrimidine (**32**) was produced from **20** and dimethylaminoacrolein (**31**). Conducting the reaction in refluxing glacial acetic acid afforded the pyrazolone **33a** and its condensation product **33b**. Further, ketones **34** ($R = \text{H, Me}$) converted **20** to the 4-phenylpyrazolo[3,4-*b*]pyridones **35** together, in one case, with the pyrimidine isomer **36**.⁴⁰

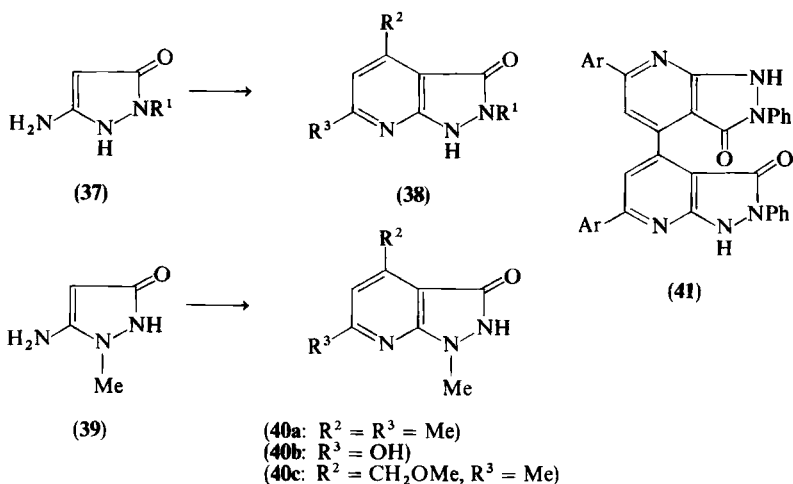
³⁶ P. Nantka-Namirski, L. Kaczmarek, R. Balicki, and M. Mordarski, Polish Patent 107,488 (1980) [C.A. **94**, 103361 (1981)].

³⁷ P. Papini, S. Checchi, and M. Ridi, *Gazz. Chim. Ital.* **87**, 931 (1957).

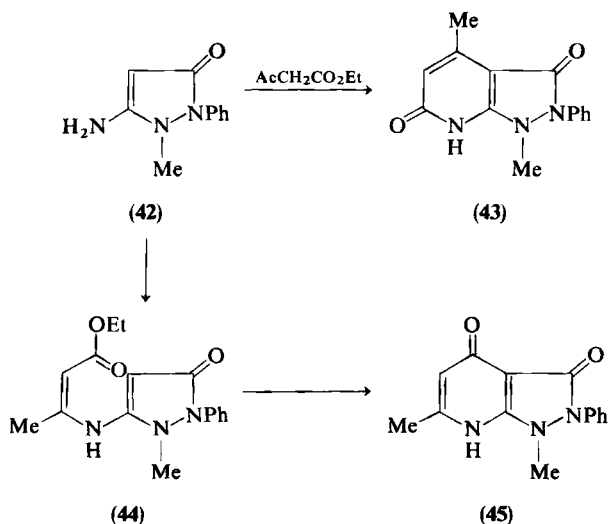
³⁸ M. Ridi, P. Papini, and S. Checchi, *Gazz. Chim. Ital.* **91**, 973 (1961).

³⁹ H. Dorn and T. Mueller, *Z. Chem.* **20**, 95 (1980).

⁴⁰ P. Nantka-Namirski and L. Kaczmarek, *Pol. J. Pharmacol. Pharm.* **30**, 563 (1978).



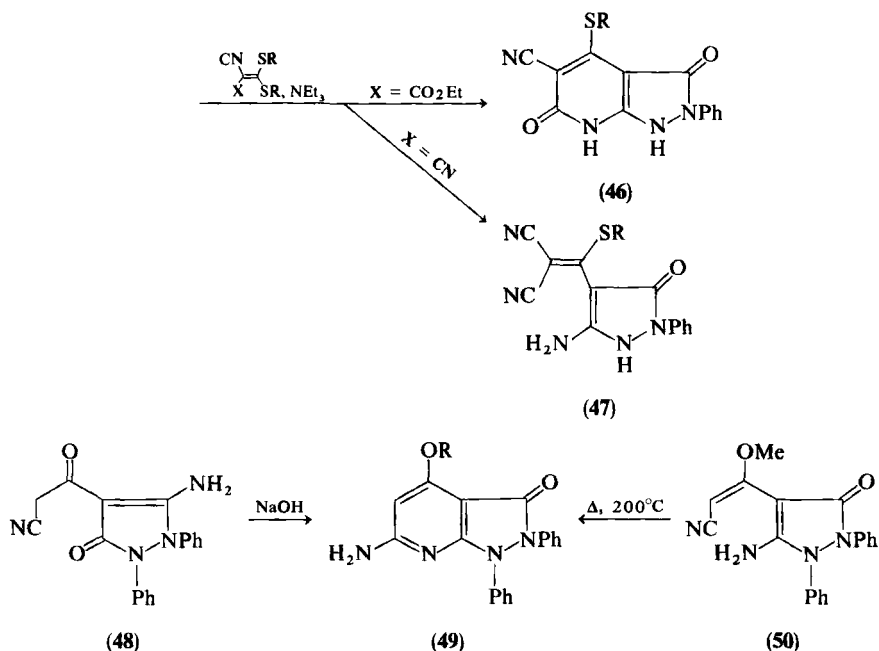
A 6-oxo bicycle (43) was also produced from base-induced cyclization of the N,N-disubstituted pyrazole 42. The isomer 45 was formed from the crotonate 44 in liquid paraffin at 250°C.⁴⁶ Analogous reactions have been reported in the aminopyrazole series (Section II,7,a).



c. *Reaction with Miscellaneous Reagents.* Treatment of pyrazolone 37 with alkenes afforded the pyridones 46. Initial attack on the pyrazole ring

⁴⁶ I. Ito, *Yakugaku Zasshi* **81**, 1738 (1961) [*CA*, **57**, 16594 (1962)].

is likely because attempts to form a 6-amino analog gave uncyclized products (47).⁴⁷ The direct formation of 4-oxopyrazolo[3,4-*b*]pyridines (49: R = H, Me) from the cyanoacetylpyrazolone 48 or its methyl ether 50 has been reported.⁴⁸



6. From 1-H-3(5)-Aminopyrazoles

Pyrazolo[1,5-*a*]pyrimidines are the usual cyclization products of N-unsubstituted 3(5)-aminopyrazoles.⁴⁹⁻⁵³ Reimlinger *et al.*,⁵⁴ however, isolated a pyrazolo[3,4-*b*]pyridine in low yield from 51 and ethyl 2-ethoxyacry-

⁴⁷ R. Gomper and W. Toepfl, *Chem. Ber.* **95**, 2871 (1962).

⁴⁸ M. A. McGee, G. T. Newbold, J. Redpath, and F. S. Spring, *J. Chem. Soc.*, 2536 (1960).

⁴⁹ S. V. Tabak, I. I. Grandberg, and A. N. Kost, *Chem. Heterocycl. Compd. (Engl. Transl.)* **1**, 79 (1965).

⁵⁰ H. Dorn, *Chem. Ber.* **101**, 3265 (1968).

⁵¹ T. Norison, J. P. Miller, M. Scholten, R. K. Robins, L. N. Simon, D. E. O'Brien, and R. B. Meyer, *J. Med. Chem.* **18**, 460 (1975).

⁵² H. Dorn and A. Zubek, *Angew. Chem., Int. Ed. Engl.* **6**, 958 (1967).

⁵³ S. Checchi, M. Ridi, and P. Papini, *Gazz. Chim. Ital.* **85**, 1558 (1955).

⁵⁴ H. Reimlinger, M. A. Peiren, and R. Mereny, *Chem. Ber.* **103**, 3252 (1970).

late or methyl acetylenecarboxylate, which was arbitrarily assigned a 4-oxo structure. This was initially accepted by Korbukh *et al.*^{55,56} but later formulated as the 6-oxo isomer **52** following a ¹³C-NMR study.⁵⁷ A similar conclusion was drawn by Dorn and Ozegowski.⁵⁸

7. From 1-Substituted 3(5)-Aminopyrazoles and 1,3-Dicarbonyl Compounds

Reagents used in the aminopyrazolone series (Section II,5) are also effective when applied to the cyclization of aminopyrazoles.

a. *1-Substituted 5-Aminopyrazoles.* 1-Substituted 5-aminopyrazoles cannot form a pyrimidine ring, and annelation with 1,3-dicarbonyl compounds furnishes pyrazolo[3,4-*b*]pyridines in good yield. For example, condensation of acetylacetone with 1,3-diphenyl-,⁵³ 1-phenyl-3-methyl-,⁴⁹ or 1,3-dimethyl-5-aminopyrazoles (**51**)⁵⁹ under acid or neutral conditions gave the 4,6-dimethyl derivatives **54** ($R^3 = R^5 = \text{Me}$, $R^4 = \text{H}$). Analogous products were formed, using diketones **53** ($R^3 = R^5 = \text{Ph, Me}$, $R^4 = \text{H, Cl, AcO}$).^{59,60} The potential for mixed-isomer formation from 1-substituted 5-aminopyrazoles and unsymmetrical 1,3-dicarbonyl compounds has led to some confusion in the literature. Depending on conditions, one of two possible regioisomers can be produced, either directly or from isolated intermediates. Tabak *et al.*⁴⁹ and Ratajczyk and Swett⁶¹ reinvestigated several reactions, and their assignments have been confirmed by independent synthesis⁶¹ or comparison of ¹³C-NMR spectra with those of model compounds.^{61,62} Thus **51** ($R^1 = \text{Me, Ph}$; $R^2 = \text{Me}$) and ethyl acetoacetate in refluxing glacial acetic acid gave pyridone **55** and not the 4-oxo isomer.^{50,52,63,64} Analogous assignments have been made by other

⁵⁵ I. A. Korbukh, F. F. Blanko, M. Preobrazhenskaya, and H. Dorn, *J. Org. Chem. USSR (Engl. Transl.)* **7**, 2739 (1971).

⁵⁶ I. A. Korbukh, F. F. Blanko, M. Preobrazhenskaya, H. Dorn, N. G. Kondakova, T. I. Sukhova, and N. P. Kostyuchenko, *J. Org. Chem. USSR (Engl. Transl.)* **9**, 1294 (1973).

⁵⁷ I. A. Korbukh, F. F. Blanko, and M. Preobrazhenskaya, *J. Org. Chem. USSR (Engl. Transl.)* **12**, 2043 (1976).

⁵⁸ H. Dorn and R. Ozegowski, *J. Prakt. Chem.* **324**, 557 (1982).

⁵⁹ Upjohn Co., British Patent 1,104,115 (1968) [*C.A.* **69**, 43906 (1968)].

⁶⁰ H. R. Snyder, *J. Heterocycl. Chem.* **12**, 1303 (1975).

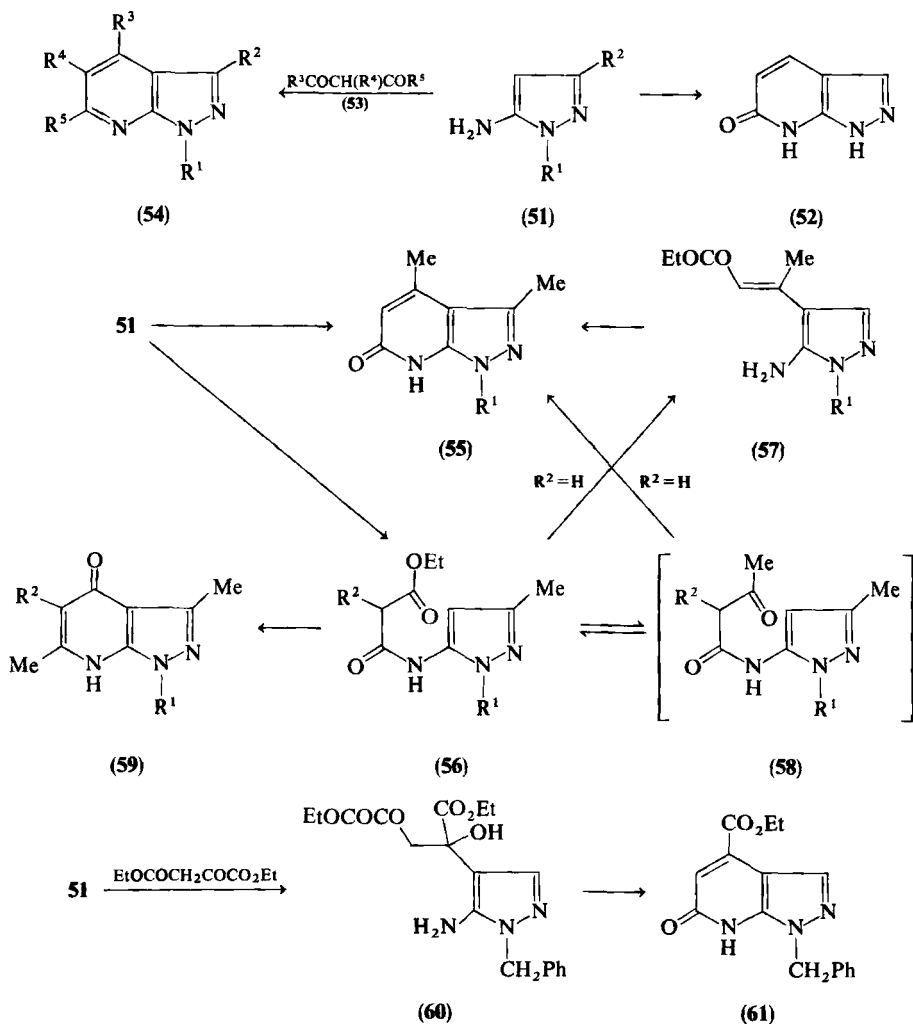
⁶¹ J. D. Ratajczyk and L. R. Swett, *J. Heterocycl. Chem.* **12**, 517 (1975).

⁶² H. Dorn and R. Ozegowski, *J. Prakt. Chem.* **321**, 881 (1979).

⁶³ C. Bulow, *Ber. Dtsch. Chem. Ges.* **43**, 3401 (1910).

⁶⁴ Y. Makisumi, *Chem. Pharm. Bull.* **10**, 617 (1962).

workers.⁶⁵⁻⁶⁸ In the reaction of **51** ($R^1 = \text{Et}$, $R^2 = \text{Me}$) with ethyl benzoylacetate in polyphosphoric acid, no evidence was given for the proposed 4-oxo structure.⁶⁹



⁶⁵ S. Checchi, M. Ridi, and P. Papini, *Gazz. Chim. Ital.* **85**, 1160 (1955).

⁶⁶ H. Dorn and R. Ozegowski, *Z. Chem.* **20**, 59 (1980).

⁶⁷ H. Dorn and R. Ozegowski, German (East) Patent 138,773 (1979) [*C.A.*, **93**, 132481 (1980)].

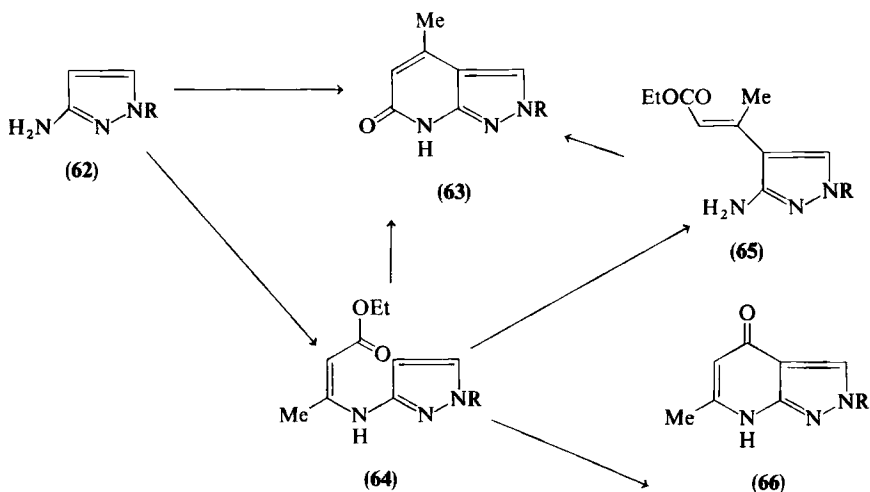
⁶⁸ V. M. Dziomko, A. V. Vaschenko, O. N. Garicheva, L. V. Shmelev, Y. S. Ryabokubylo, and G. M. Adamova, *Chem. Heterocycl. Compd. (Engl. Transl.)* **17**, 715 (1981).

⁶⁹ H. Hoehn and E. Schulze, U.S. Patent 3,894,005 (1975) [*C.A.*, **84**, 17333 (1976)].

Crotonate intermediates (**56**: $R^2 = H$) have been heated in glacial acetic acid⁶¹ or ethylene glycol⁴⁹ or its monomethyl ether⁶¹ to afford products of direct cyclization (**55**). Isomeric pyridones (**59**: $R^1 = Me, Ph$), however, were obtained using hot Dowtherm.^{49,61}

Similarly, cyclization of **56** ($R^1 = Et, R^2 = Cl, SO_2Ph$) in refluxing diphenyl ether gave the corresponding 6-oxo isomers **55**.^{70,71} Tabak *et al.*⁴⁹ suggest an equilibrium between crotonate **56** and amide **58** because, in the benzenoid series,⁷² the analogous amide is the favored structure in acid solution. Dorn and Ozekowski,^{58,62} however, observed a similar dependence on conditions but interpreted the results in terms of the vinylpyrazoles **57**, formed as by-products in the acid-catalyzed conversion of **56** ($R^2 = H$) to the 6-oxo compounds **55** ($R^1 = Me, CH_2Ph$). Dorn and Mueller³⁹ also report isolation of pyrazole **60** during the preparation of the bicyclic ester **61** from **51**. (Compound **61** was formerly believed^{73,74} to be the 4-oxo isomer on the basis of its conversion to the erroneously assigned⁴⁹ 4-oxo-6-methyl derivative.)

b. *1-Substituted 3-Aminopyrazoles*. 1-Substituted 3-aminopyrazole should prove less reactive than the 5-amino isomers.⁶² Nevertheless, 2-substituted pyrazolo[3,4-*b*]pyridines have been prepared under similar conditions to those discussed in the previous section. For example, **62** ($R = Me$,



⁷⁰ T. Denzel and H. Hoehn, U.S. Patent 3,847,929 (1974) [*CA*, **82**, 57685 (1975)].

⁷¹ T. Denzel and H. Hoehn, U.S. Patent 3,903,096 (1975) [*CA*, **83**, 206257 (1975)].

⁷² C. R. Hauser and G. A. Reynolds, *J. Am. Chem. Soc.* **70**, 2402 (1948).

⁷³ S. Checchi, P. Papini, and M. Ridi, *Gazz. Chim. Ital.*, **86**, 631 (1956).

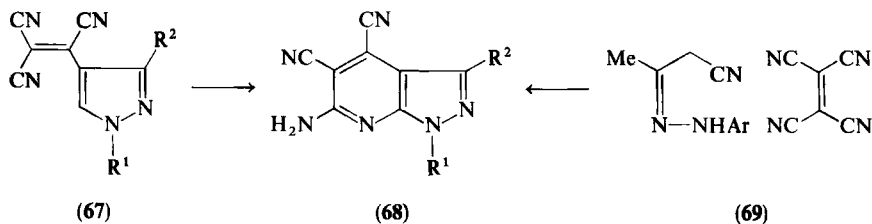
⁷⁴ H. Dorn and A. Zubek, *Pharmazie* **26**, 732 (1971).

Ph, CH₂Ph)^{66,75} and ethyl acetoacetate under acidic conditions afforded the 6-oxo derivatives **63**, also produced from the crotonates **64** by heating in acid or 1,2-dimethoxyethane.^{62,66} Dorn and Ozekowski⁶⁶ observed rearrangement of **64** (R = Me, CH₂Ph) to the vinylpyrazoles **65**, which cyclized in refluxing ethanol. The isomeric pyridone **66** was obtained by heating the crotonate **64** (R = Ph) in Dowtherm.⁴⁹

8. Miscellaneous Cyclizations of 3(5)-Aminopyrazoles

The tricyanovinylpyrazoles **67**, isolated from reaction of tetracyanoethylene (TCNE) with **51** (R¹ = H, Ph; R² = H, Me), cyclized in refluxing acetic anhydride to **68**.⁷⁶ Analogous products (**68**: R¹ = Ar, R² = Me) were obtained from thermolysis or photolysis of the charge-transfer complex **69** formed between TCNE and arylhydrazones.⁷⁷

Numerous patents^{78,79} have recorded the preparation of malonates (**71**: X = CO₂Et), which afforded 4-hydroxy or 4-chloro derivatives (**72**: R³ = OH, Cl) when refluxed with diphenyl ether or phosphorous oxychloride. The reaction has provided 2-substituted isomers^{80,81} from 3-aminopyrazoles and, by using the appropriate reagent (**70**: X = COR), the corresponding 5-ketones (**72**) can be obtained.⁸²⁻⁸⁷



⁷⁵ H. Dorn and R. Ozegowski, *Z. Chem.* **20**, 17 (1980).

⁷⁶ H. Junek and H. Aigner, *Chem. Ber.* **106**, 914 (1973).

⁷⁷ H. Junek, A. Hermelter, H. Fischer-Colbrie, M. Wittmer-Metz, and A. M. Braun, *Chem. Ber.* **109**, 1787 (1976).

⁷⁸ H. Hoehn, T. Denzel, and W. Jannssen, *J. Heterocycl. Chem.* **9**, 235 (1972), and references quoted therein.

⁷⁹ I. Chu and B. M. Lynch, *J. Med. Chem.* **18**, 161 (1975).

⁸⁰ T. Denzel and H. Hoehn, Ger. Offen. 2,617,157 (1976) [*CA.* **86**, 55433 (1973)].

⁸¹ T. Denzel and H. Hoehn, U.S. Patent 4,038,238 (1977) [*CA.* **87**, 168026 (1977)].

⁸² H. Hoehn, Ger. Offen. 2,225,433 (1971) [*CA.* **78**, 84404 (1973)].

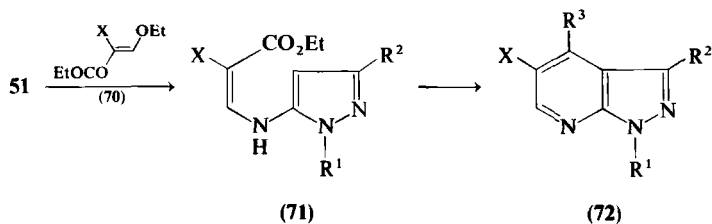
⁸³ T. Denzel and H. Hoehn, U.S. Patent 3,780,047 (1973) [*CA.* **80**, 83082 (1974)].

⁸⁴ T. Denzel, H. J. Schneider, and H. Hoehn, U.S. Patent 3,987,051 (1976) [*CA.* **86**, 43702 (1977)].

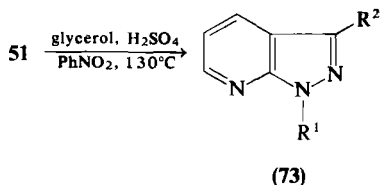
⁸⁵ H. Hoehn and T. Denzel, Ger. Offen. 2,333,603 (1974) [*CA.* **80**, 108514 (1974)].

⁸⁶ T. Denzel and H. Hoehn, U.S. Patent 3,985,757 (1975) [*CA.* **86**, 29805 (1977)].

⁸⁷ T. Denzel and H. Hoehn, *Arch. Pharm. (Weinheim, Ger.)* **309**, 486 (1976)].



The Skraup reaction and Friedlander synthesis have found application in the preparation of pyrazolo[3,4-*b*]pyridines. Cyclization of 1-benzyl-5-aminopyrazoles (**51**: $R^1 = \text{CH}_2\text{Ph}$; $R^2 = \text{H, Me}$)^{88,89} under usual Skraup conditions gave the 1-benzyl derivatives (**73**) in moderate yield. The 1-*H* derivative (**73**, $R^1 = \text{H}$, $R^2 = \text{Ph}$), however, was isolated only in poor yield.⁸⁹



Using a modification of the Friedlander synthesis, the aminopyrazolecarboxylate **74a** was converted to the bicyclic pyridone (**75**: $R^1 = \text{OH}$, $R^2 = \text{CO}_2\text{Et}$).⁹⁰ In a series of analogous reactions^{90,91} the amines (**75**: $R^1 = \text{NH}_2$; $R^2 = \text{CN, CO}_2\text{Et}$) were obtained from cyanopyrazole **74b** and the appropriate 1,3-dicarbonyl compound. In addition, the carboxaldehyde **74c** reacted with ketones to afford 5,6-substituted derivatives (**76**: $R^1 = \text{Me, Ph}$; $R^2 = \text{H, CO}_2\text{Et}$; $R^3 = \text{Me, Ph}$).^{61,92} When pyrazole carboxylate **74a** was treated with benzyl cyanide, the pyrazolo[3,4-*b*]pyridine **77** was isolated as a by-product.⁹³ An interesting example of the Friedlander synthesis was provided by reaction of **51** with acetic anhydride, in which the products (**79**: $R = \text{H, Ac}$) were believed to arise by intermolecular condensation of ketone **78**.⁹⁴

⁸⁸ R. Dorgan, J. Parrick, and C. R. Hardy, *J. C. S. Perkin Trans. I*, 938 (1980).

⁸⁹ I. I. Grandberg, *Zh. Obshch. Khim.* **37**, 2307 (1961) [*CA*, **56**, 3472 (1962)].

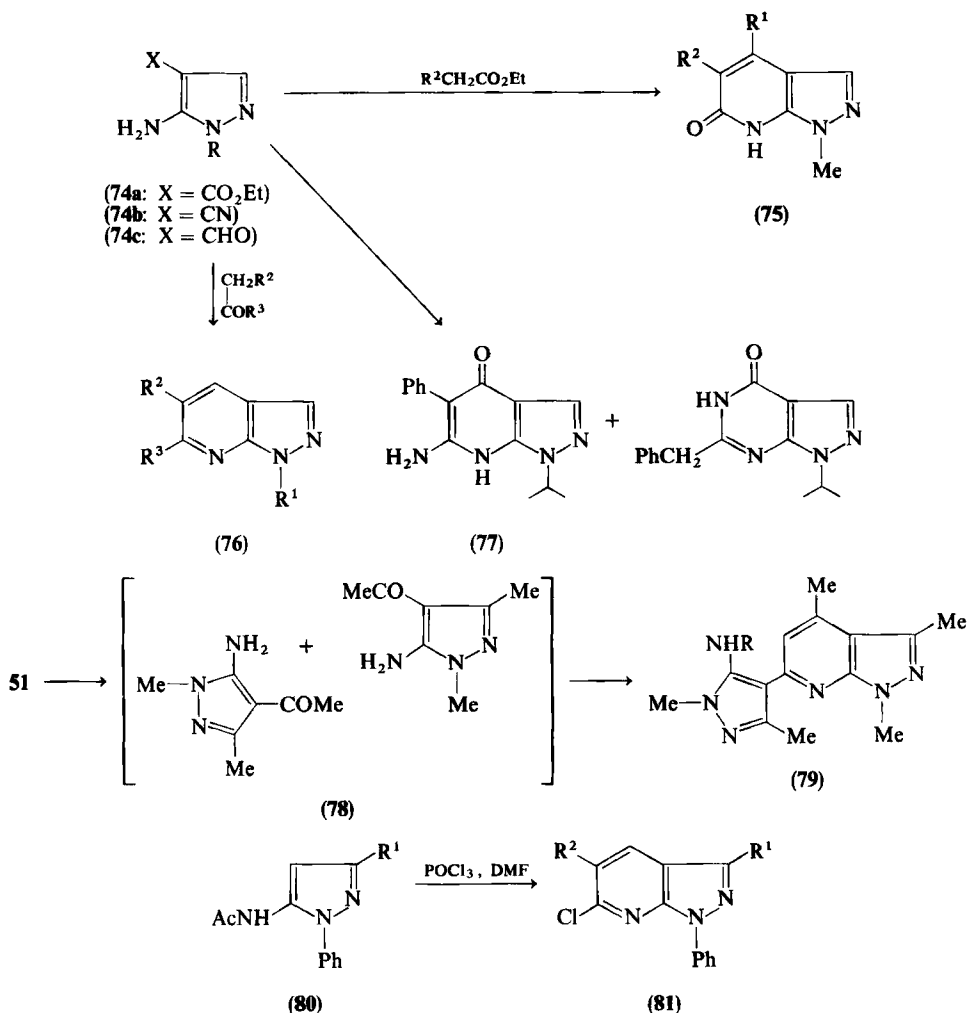
⁹⁰ S. W. Schneller and D. R. Moore, *J. Heterocycl. Chem.* **15**, 319 (1978).

⁹¹ K. Gewald, H. Schaefer, and K. Sattler, German (East) Patent 143,426 (1980) [*CA*, **95**, 25039 (1981)].

⁹² T. Higashino and Y. Iwai, *Chem. Pharm. Bull.* **25**, 535 (1977).

⁹³ P. Schmidt, K. Eichenberger, and M. Wilhelm, *Helv. Chim. Acta* **45**, 1620 (1962).

⁹⁴ E. Gonzalez, R. Sarlin, and J. Elguero, *Tetrahedron* **34**, 1175 (1978).

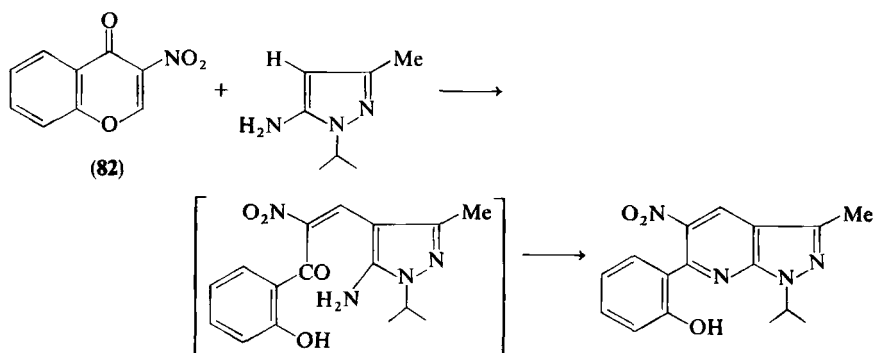


Under controlled conditions, the acetylaminopyrazole **80** was converted by Vilsmeier–Haack reaction to a mixture of chloro derivatives (**81**: R² = H, CHO) in poor and moderate yields, respectively. Cyclization is preceded by C-formylation and formation of the imidoyl chloro group.⁹⁵

The electrophilic sites in 3-nitrochromone (**82**) provide a three-carbon fragment for cyclization of 5-aminopyrazoles. A mechanism has been suggested (Scheme 1).⁹⁶

⁹⁵ A. Simeny, K. Takaes, and L. Toth, *Acta Chim. Acad. Sci. Hung.* **109**, 175 (1982).

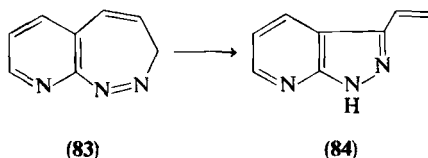
⁹⁶ G. Haas, J. L. Stanton, and T. Winkler, *J. Heterocycl. Chem.* **18**, 619 (1981).



SCHEME 1

9. From Other Heteroarenes

a. *Pyridodiazepines*. Tsuchiya *et al.*⁹⁷ photolyzed pyridodiazepine **83** in dichloromethane or methanol to furnish the 3-vinyl derivative **84**. The yield was improved by thermolysis of **83** in refluxing xylene.



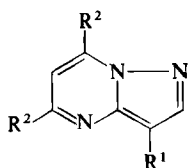
b. *Pyrazolopyrimidines*. Decarboxylative acid hydrolysis of suitably substituted pyrazolopyrimidines provides a route to the parent pyrazolo-[3,4-*b*]pyridines. Khan and Lynch⁹⁸ reported thermal decarboxylation of the acid **85a** to the major product (**1**), which was also obtained as sole product in 80% yield from acid hydrolysis of the cyano compound **85b**. The dimethyl derivative **85c** afforded none of the rearranged product. The parent and 5,7-dimethylpyrazolo[1,5-*a*]pyrimidines are stable under the conditions used to effect rearrangement,^{98,99} but a nitro group in the pyrimidine ring facilitated hydrolysis, allowing formation of **86**.⁹⁹ Likewise, the amides **87**,⁹⁹ **88**,¹⁰⁰ and **38** [$R^1 = H$, $R^2 = CF_3(Me)$, $R^3 = Me(CF_3)$]³² were prepared by isomerization in sodium hydroxide solution.

⁹⁷ T. Tsuchiya, M. Enkaku, and H. Sawanishi, *Chem. Pharm. Bull.* **27**, 2188 (1979).

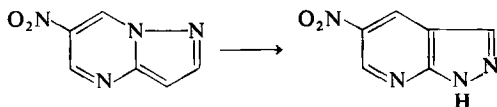
⁹⁸ M. A. Khan and B. M. Lynch, *J. Heterocycl. Chem.* **7**, 247 (1970).

⁹⁹ A. N. Kost, R. S. Sagitullin, and G. G. Danagulyan, *Chem. Heterocycl. Compd. (Engl. Transl.)* **13**, 454 (1977).

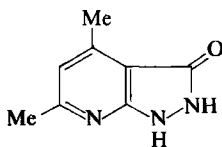
¹⁰⁰ H. Hoehn, U.S. Patent 4,048,184 (1976) [*CA*, **88**, 6078 (1978)].



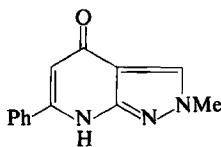
- (85a: R¹ = CO₂H, R² = H)
 (85b: R¹ = CN, R² = H)
 (85c: R¹ = CO₂H, R² = Me)



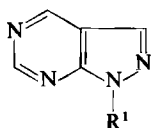
(86)



(87)



(88)



(89)

Higashino *et al.* have exploited the reaction between active methylene compounds and pyrazolo[3,4-*d*]pyrimidines (89) (as free base,¹⁰¹ N-oxide,^{102,103} or salts^{92,101}) to prepare a large number of 6,7-substituted derivatives (54: R² = R³ = H). A mechanism was suggested.⁹²

10. From Acyclic Compounds

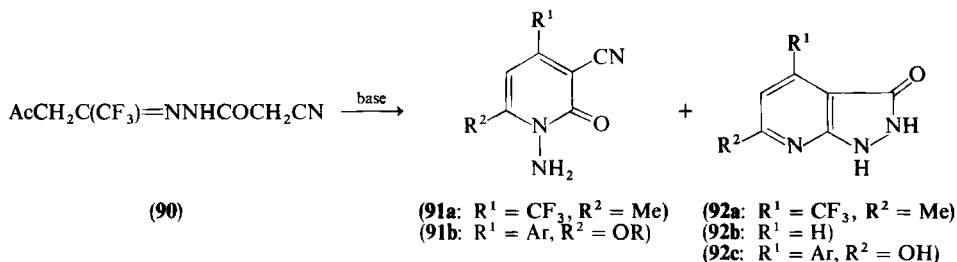
Michael-type condensation of cyanoacetohydrazide (NCCH₂CONHNH₂, CAH) with 1,3-dicarbonyl compounds gave pyrazolo[3,4-*b*]pyridines under certain conditions. With 1,1,1-trifluoropentane-2,4-dione in the presence of piperidine a 1:3 mixture of pyrazolone 92a and the expected aminopyridone 91a was obtained.¹⁵ The bicycle was also obtained from hydrazone (90) or by thermal reaction between its two precursors.³² Reaction of CAH and β-keto aldehydes gave good yields of only bicyclic products 92b,²⁰ whereas ethyl benzoylacetate in the presence of piperidine gave bicycle 92c (Ar = Ph)

¹⁰¹ T. Higashino, Y. Iwai, and E. Hayashi, *Hokusokan Kagaku Toronkai Koen Yoshishu*, 8th, 199 (1975) [*C.A.* **84**, 16471 (1976)].

¹⁰² T. Higashino, Y. Iwai, and E. Hayashi, *Chem. Pharm. Bull.* **24**, 3120 (1976).

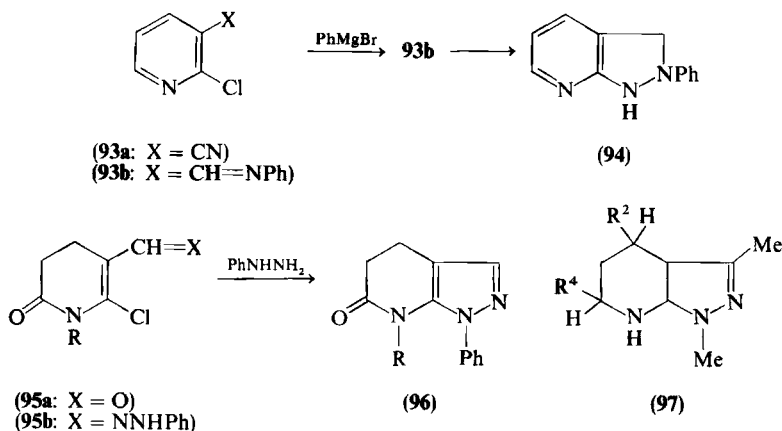
¹⁰³ T. Higashino, K. Suzuki, and E. Hayashi, *Chem. Pharm. Bull.* **26**, 3485 (1978).

and pyridone **91b** ($R = H$, $Ar = Ph$) in low yield, the major product being 3-amino-5-pyrazolone (**20**).¹⁰⁴ Interestingly, use of potassium hydroxide in the last reaction gave mainly the potassium salt of aminopyridones (**91b**: $R = K$, $Ar = Ph, p\text{-NO}_2Ph$), which on acidification produced the corresponding **92b** as minor or major components, respectively.¹⁰⁴



B. SYNTHESIS OF REDUCED PYRAZOLO[3,4-*b*]PYRIDINES

The anil **93b**, prepared from the corresponding cyanopyridine **93a**, when treated with hydrazine, afforded the dihydro derivative **94**.¹⁰⁵



The reduced pyridones **96** were obtained in good yield from the aldehydes **95a** directly¹⁰⁶ or via the phenylhydrazones **95b**.¹⁰⁷ Platinum oxide-catalyzed hydrogenation of the pyridine ring in **16** gave tetrahydro products (**97**: $R^2 = \text{Me}, H$; $R^4 = H, \text{Me}$).⁶¹

¹⁰⁴ R. Balicki and P. Nantka-Namirski, *Pol. J. Chem.* **53**, 2225 (1979).

¹⁰⁵ H. Jabine, H. A. Zaher, M. Seada, and M. F. Ishak, *Indian J. Chem. Sect. B* **17B**, 134 (1979).

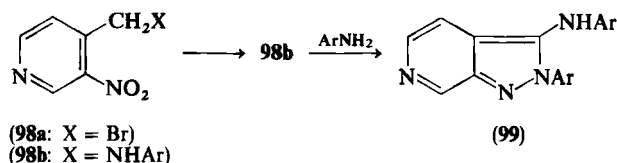
¹⁰⁶ M. Weissenfels and S. Kaubisch, *Z. Chem.* **22**, 23 (1982).

¹⁰⁷ M. Weissenfels and S. Kaubisch, *Z. Chem.* **21**, 259 (1981).

C. SYNTHESIS OF PYRAZOLO[3,4-*c*]PYRIDINES

1. From 3-Nitropyridines

3-Nitropyridines containing an adjacent bromomethyl substituent react with aromatic primary amines to give pyrazolo[3,4-*c*]- and -[4,3-*b*]pyridines. The intermediate secondary amines **98b** undergo further reaction at elevated temperatures to afford arylamino derivatives **99** in good yield.¹⁰⁸ A mechanism has been proposed for the analogous formation of pyrazolo[4,3-*b*]pyridines (Section II.G,1).¹⁰⁹



2. From 3-Nitrosaminopyridines

Pyrazolo[3,4-*c*]- and -[4,3-*b*]pyridines are also available from intramolecular cyclization of *o*-methyl-3-nitrosaminopyridines. The nitrosamines **100b** are generated with NOCl in acetic anhydride and cyclized, without isolation, to 1- (**101**) and/or 2-acyl (**102**) derivatives depending on the substituents in the pyridine ring. 6-Methyl- or 6-methoxynitrosamines (**100b**: R¹ = Me, OMe; R² = H), for example, gave good yields of 1-acyl products **101** only, whereas 6-chloro- or 2-methoxynitrosamines (**100b**: R¹ = Cl, H; R² = H, OMe) produced mixtures of the corresponding acyl derivatives. Dilute acid hydrolysis of **101** and **102** afforded the 1-*H* derivatives. Under these conditions, the 5-methoxy compound **101** (R¹ = OMe, R² = H) underwent hydrolysis to the pyridone **103**. However, the desired 5-methoxy-1-*H* derivative was obtained by conducting the nitrosation step in the absence of acetic anhydride. The 7-chloro analog was also obtained, in low yield, by adopting this procedure.¹¹⁰ The parent heterocycle has been prepared in 82% yield by this route.¹¹¹ A mechanism was proposed¹¹⁰ by analogy with reactions in the indazole series,¹¹² involving elimination of acetic acid from a dia-

¹⁰⁸ J. Hurst and D. G. Wibberley, *J. Chem. Soc. C*, 1487 (1968).

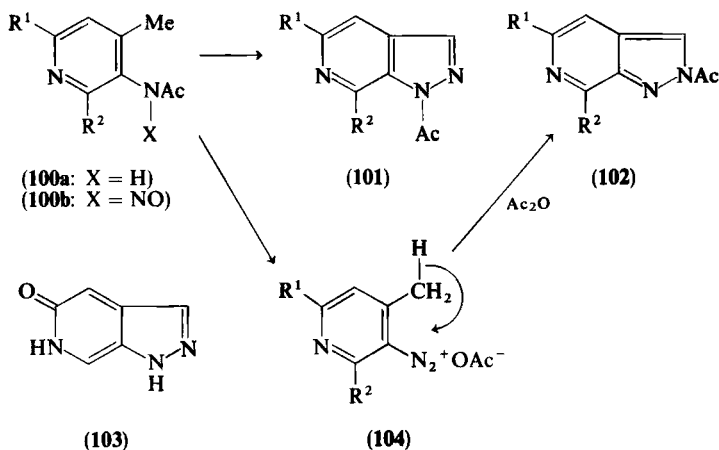
¹⁰⁹ H. E. Foster and J. Hurst, *J. C. S. Perkin Trans. I*, 319 (1973).

¹¹⁰ D. Chapman and J. Hurst, *J. C. S. Perkin Trans. I*, 2398 (1980).

¹¹¹ H. E. Foster and J. Hurst, *J. C. S. Perkin Trans. I*, 2901 (1973).

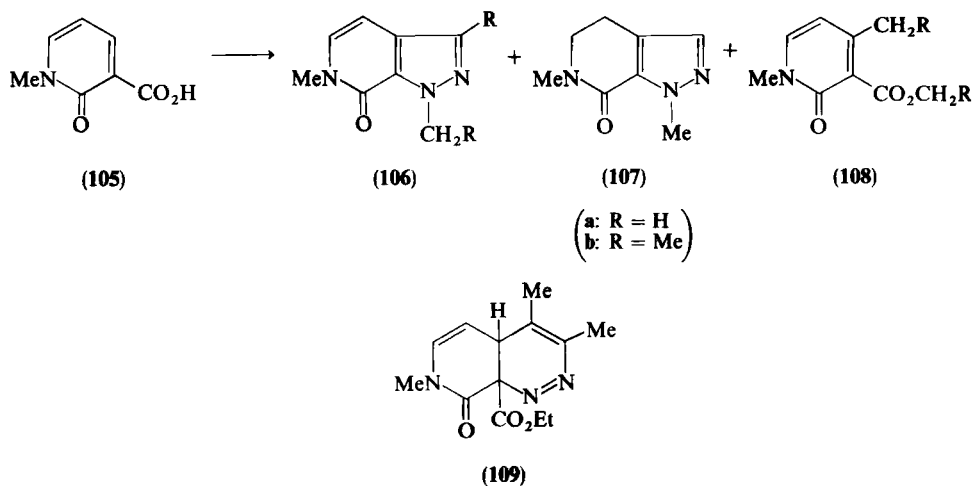
¹¹² B. H. Klandermann, D. P. Maier, G. W. Clark, and J. A. Kampmeier, *J. C. S. Chem. Commun.*, 1003 (1971).

zonium salt (104). The conversion of 4-methylpyridine 3-diazonium salts to pyrazolo[3,4-*c*]pyridines has been reported.¹¹³



3. From Nicotinic Acid Derivatives

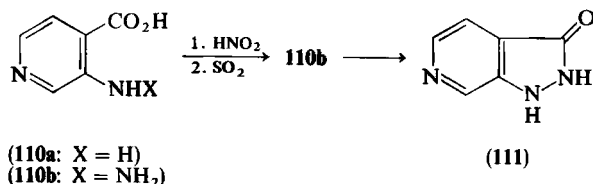
When the nicotinic acid derivative **105** was treated with diazomethane, a mixture of products was formed. The bicyclic products were produced by independent routes because dehydrogenation of **107** could not be achieved.



¹¹³ S. Furukawa, *J. Pharm. Soc. Jpn.* **76**, 900 (1956).

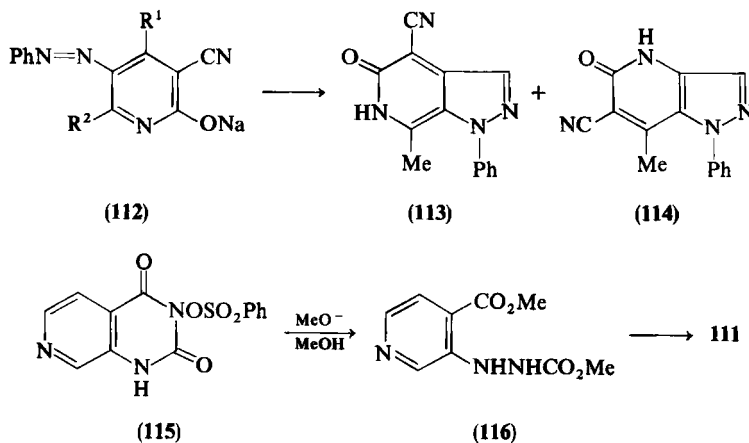
Further, reaction of **105** with diazoethane gave **106b** and **108b** as major products together with the bicycle **109**.¹¹⁴

Diazotization and reduction of 3-aminoisonicotinic acid (**110a**) yielded hydrazinopyridine **110b**, which underwent acid-catalyzed cyclization to the pyridone **111**.¹⁹



4. From Phenylazopyridines

The azopyridines **112** ($\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{CH}_2\text{OMe}$; and $\text{R}^1 = \text{CH}_2\text{OMe}$, $\text{R}^2 = \text{Me}$) were cyclized together in glacial acetic acid to the pyrazolo[3,4-*c*]- (**113**) and -[4,3-*b*]pyridines (**114**), which were analyzed as a mixture. The phenyl substituent was arbitrarily assigned to the 1-position.¹¹⁵



Likewise, acid-catalyzed cyclization of the 3-hydrazinopyridine **116**, produced by Hoffmann cleavage of pyridopyrimidione **115**, gave pyrazolone **111** in excellent yield.¹¹⁶

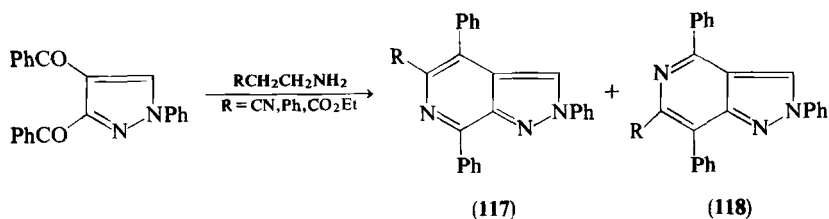
¹¹⁴ T. Kametani, Y. Kigawa, T. Takahashi, H. Nemoto, and K. Fukumoto, *Chem. Pharm. Bull.* **24**, 1870 (1976).

¹¹⁵ S. Ulrich, *Justus Liebigs Ann. Chem.* **657**, 156 (1962).

¹¹⁶ K. Y. Tserng and L. Bauer, *J. Heterocycl. Chem.* **11**, 163 (1974).

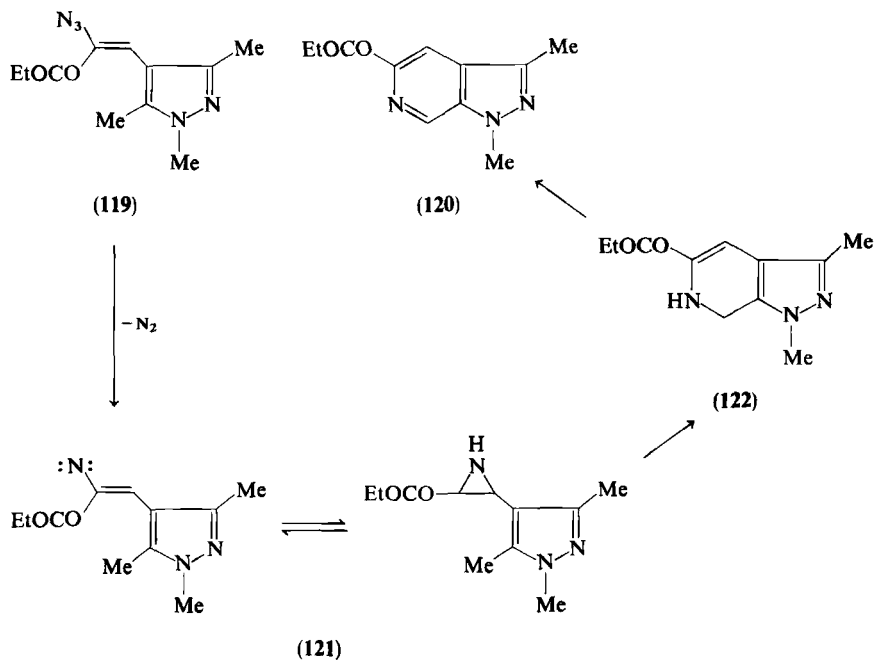
5. From 3,4-Dibenzoylpyrazole

Treatment of 3,4-dibenzoylpyrazole with amines in refluxing ethanol furnished mixtures of 5-substituted pyrazolo[3,4-*c*]- (117) and 6-substituted pyrazolo[4,3-*c*]pyridines (118).¹¹⁷ The latter isomer was the major constituent in each case and the structures were assigned, using NMR spectrometry.



6. From Azidovinylpyrazoles

Thermal decomposition of azidovinylpyrazole 119 in refluxing bromobenzene afforded the ester 120 in moderate yield. The position of the *N*-methyl

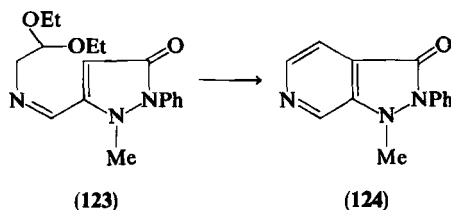


¹¹⁷ S. Mataka, K. Takahashi, and M. Tashiro, *J. Heterocycl. Chem.* **18**, 1073 (1981).

substituent was deduced by comparison of UV and $^1\text{H-NMR}$ spectra with those of model compounds.¹¹⁸ Evidence is given for the formation of a nitrene \rightleftharpoons azirine intermediate (**121**), which cyclizes to dihydro compound **122**.

7. From Iminomethylpyrazolones

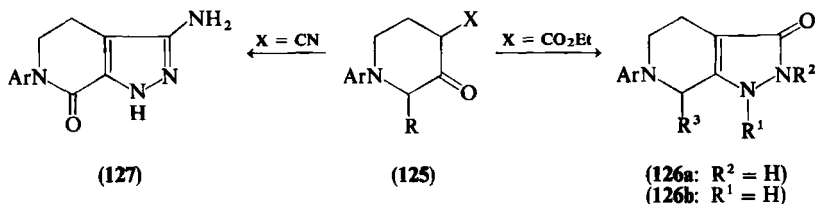
An N,N-disubstituted pyrazolo[3,4-*c*]pyridone (**124**) was isolated from acid-catalyzed cyclization of the acetal **123**.⁴⁶



D. SYNTHESIS OF REDUCED PYRAZOLO[3,4-*c*]PYRIDINES

1. From 3-Piperidones

A number of reduced pyrazolo[3,4-*c*]pyridines have been prepared by cyclization of 3-piperidones substituted in the 4-position. For example, reaction of 4-ethoxycarbonyl- or 4-cyano-3-piperidones (**125**: X = CO₂Et or CN) with hydrazine afforded the pyrazolones **126a** (R¹ = H)¹¹⁹ or amines **127**,¹²⁰ respectively.



Substituted hydrazines provide 1- and/or 2-substituted derivatives depending on the nature of **125**. Thus the dione **125** (X = CO₂Et, R = =O) and phenylhydrazine gave a mixture of isomers **126a** and **126b** (R¹ or

¹¹⁸ T. L. Gilchrist, C. W. Rees, and J. A. R. Rodrigues, *J. C. S. Chem. Commun.*, 627 (1979).

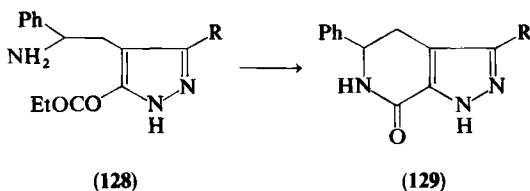
¹¹⁹ Z. Ozdowska and B. Szczycinski, *Rocz. Chem.*, **50**, 1771 (1976).

¹²⁰ H. M. Blatter, U.S. Patent 3,423,414 (1969) [*C.A.* **70**, 68361 (1969)].

$R^2 = \text{Ph}$),¹²¹ whereas the 2-phenyl derivative **126b** ($R^2 = \text{Ph}$) was the sole product from **125** ($R = \text{CH}_2\text{CH}_2\text{CO}_2\text{Et}$, $X = \text{CO}_2\text{Et}$).^{122,123} No explanation was given for the latter assignment, but the product is analogous to those obtained in the reduced pyrazolo[4,3-*c*]pyridine series (Section II,F,1).

2. From 4-Aminoethylpyrazole

4-Aminoethylpyrazoles **128** were generated *in situ* by catalytic hydrogenation of the corresponding oximes and, on treatment with base, cyclized to the pyridones **129** ($R = \text{Me}, \text{Ph}$).¹²⁴



E. SYNTHESIS OF PYRAZOLO[4,3-*c*]PYRIDINES

Although routes to this ring system are well established, the parent bi-cycle is unknown.

1. From 4-Hydrazinopyridines

Several derivatives have been prepared by acid-catalyzed cyclization of 4-hydrazinopyridines containing a carboxylic acid function. For example, cyclization in dilute acids of **130**¹²⁵ or **131a** ($R = \text{H}, \text{Ar}$)^{19,126-128} gave the 3-hydroxypyrazolo[4,3-*c*]pyridines **132** ($R^1 = \text{Ar}, R^2 = \text{H}$) or N-oxides **133**

¹²¹ CIBA Ltd., Neth. Patent Appl. 6,511,645 (1965) [*CA*. **65**, 2269 (1966)].

¹²² C. J. Bosch, S. S. Bonjoch, R. C. Martinez, and P. F. Rabadon, Spanish Patent 477,366 (1979) [*CA*. **93**, 168264 (1980)].

¹²³ C. J. Bosch and S. S. Bonjoch, *J. Org. Chem.* **46**, 1538 (1981).

¹²⁴ O. Migliara, S. Petruso, and V. Sprio, *J. Heterocycl. Chem.* **16**, 577 (1979).

¹²⁵ V. J. Ram, *J. Indian Chem. Soc.* **50**, 811 (1973).

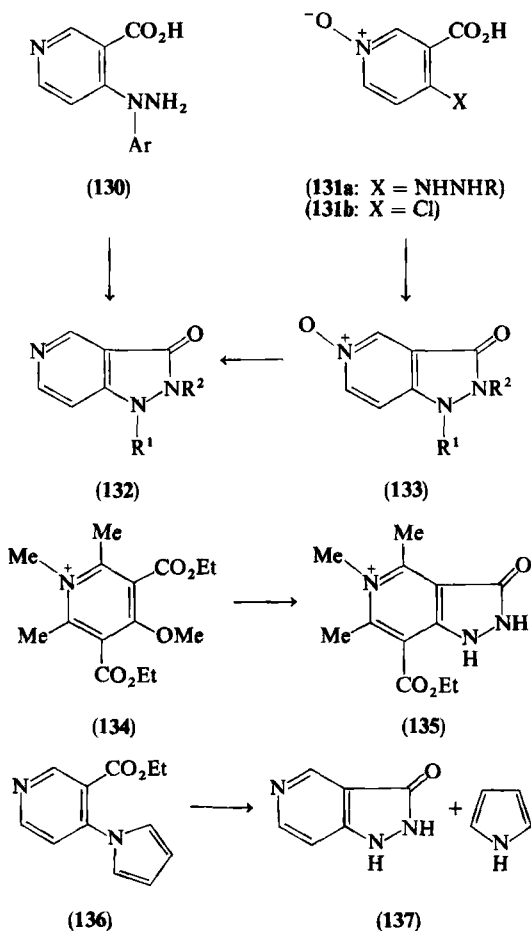
¹²⁶ R. D. Rao, *Labdev, Part A* **6**, 214 (1968).

¹²⁷ V. J. Ram and R. D. Rao, *Indian J. Appl. Chem.* **33**, 390 (1970); R. D. Rao and J. N. Singh, *Labdev, Part A*, **7**, 126 (1969).

¹²⁸ G. M. Badger and R. R. Pratap, *Aust. J. Chem.* **18**, 379 (1965).

($R^1 = \text{Ar}, R^2 = \text{H}$), which were deoxygenated in one instance.¹²⁹ Other N-oxides (**133**: $R^1 = \text{Ar}, R^2 = \text{H}$ and $R^1 = R^2 = \text{Ph}$) were obtained directly by hydrazinolysis of the 4-chloropyridine **131b**.¹²⁶ Reaction of hydrazine with the pyridinium salt **134** caused replacement of the methoxy group with formation of **135**¹²⁹ and, more unexpectedly, 3-carbethoxy-4-pyrrolylpyridine (**136**) and hydrazine afforded an almost quantitative yield of **137** by expulsion of the pyrrole nucleus.¹³⁰

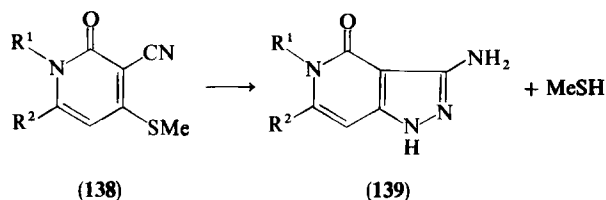
In analogous reactions, a number of 3-cyano-4-methylthiopyridones (**138**) were converted to the bicyclic amines **139** ($R^1 = \text{H}, \text{Me}, R^2 = \text{Me}, \text{Ar}$).¹³¹



¹²⁹ M. Tisler, B. Stanovnik, and Z. Zrimsek, *Heterocycles* **13**, 217 (1979).

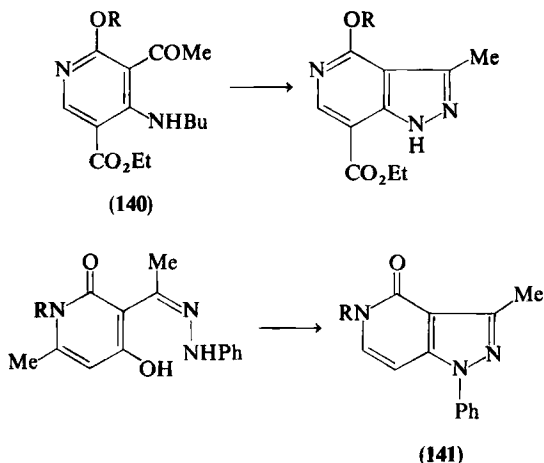
¹³⁰ S. Hunig and G. Kobrich, *Justus Liebigs Ann. Chem.* **617**, 181 (1958).

¹³¹ A. Kumar, H. Ila, and H. Junjappa, *J. C. S. Perkin Trans. 1*, 857 (1978).



2. From 3-Acetylpyridines

Treatment of 3-acetylpyridines (**140**, R = H, Et) with hydrazine in refluxing glacial acetic acid produced the N-unsubstituted bicycles.¹³² 1-Phenyl derivatives **141** (R = H, Me, Ph), however, were provided from acid-catalyzed cyclization of the corresponding hydrazones.^{133,134}



3. From Pyrazoles Containing Carboxylic Acid Functions

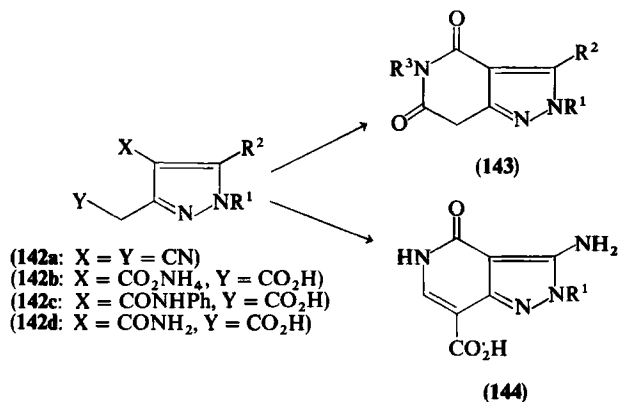
In the annelation of pyrazole-3 (or 5)-acetonitriles or -acetic acids, a cyano or carboxamido substituent in the 4-position is necessary to supply the nitrogen atom of the pyridine ring. The majority of reports concern the formation of 2-substituted products. Thus cyclization of the nitriles **142a**

¹³² N. S. Vulfson and G. M. Sukhotina, *Metody Poluch. Khim. Reakt. Prep.* **14**, 127 (1966) [*CA.* **67**, 3024 (1967)].

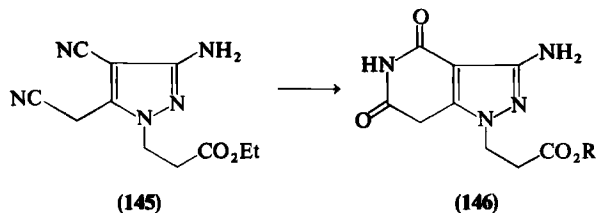
¹³³ N. S. Vulfson and G. M. Sukhotina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1785 (1966) [*CA.* **66**, 94944 (1967)].

¹³⁴ T. Denzel and H. Hoehn, *Arch. Pharm. (Weinheim. Ger.)* **306**, 746 (1973).

($R^1 = \text{H, Me, Ph, } R^2 = \text{NH}_2$) in mineral acids gave the 3-amino derivatives **143** ($R^2 = \text{H}$).¹³⁵⁻¹³⁸ The compounds **143** ($R^1 = R^2 = \text{Ph, } R^3 = \text{H or Ph}$) were obtained from the pyrazoles **142b** or **142c** ($R^1 = R^2 = \text{Ph}$) by heating in vacuo or by treatment with acetyl chloride, respectively.¹³⁹ The use of triethyl orthoformate converted the amide **142d** ($R^1 = \text{H, } R^2 = \text{NH}_2$) to the 7-carboxylic acid **144**.¹³⁹



El-Sayed and Ohta¹⁴⁰ applied the reaction to the formation of 1-substituted pyrazolo[4,3-*c*]pyridones. Dicyanopyrazole **145** was cyclized under acid or basic conditions to furnish the ester or acid **146** ($R = \text{Et or H}$, respectively). An N-unsubstituted product was obtained by heating the ester **147** with ammonia in a steel bomb.¹⁴¹



¹³⁵ M. H. Elngadi, E. A. Hafez, H. A. El-Fakham, and E. A. Kandeeel, *J. Heterocycl. Chem.* **17**, 73 (1980).

¹³⁶ T. Sato, *J. Org. Chem.* **24**, 963 (1959).

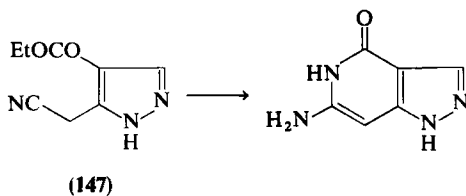
¹³⁷ E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.* **81**, 2452 (1959).

¹³⁸ E. C. Taylor and K. S. Hartke, *J. Am. Chem. Soc.* **81**, 2456 (1959).

¹³⁹ M. D. Nair, S. R. Mehta, and S. M. Kalbag, *Indian J. Chem.* **5**, 464 (1967).

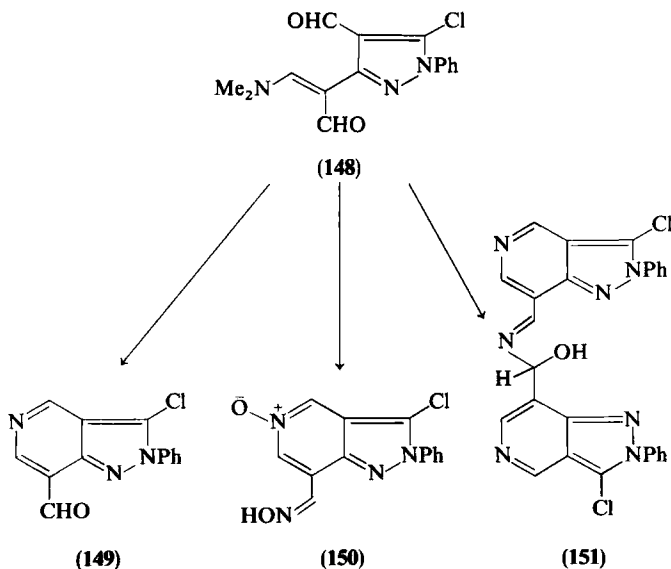
¹⁴⁰ A. A. El-Sayed and M. Ohta, *Bull. Chem. Soc. Jpn.* **46**, 1801 (1973).

¹⁴¹ R. Honna, M. Tanaka, S. Hashimoto, and T. Suzue, Japanese Kokai 83,394 (1972) [*CA.* **88**, 37791 (1978)].



4. From Vinylpyrazoles

Pyrazoles substituted with an aminovinyl or isocyanatovinyl group are useful precursors. For example, the Vilsmeier formylation product **148** on treatment with ammonium chloride, hydroxylamine, or ammonium acetate affords the aldehyde **149**, oxime **150**, or the 7,7'-dimer **151**, respectively.¹⁴²



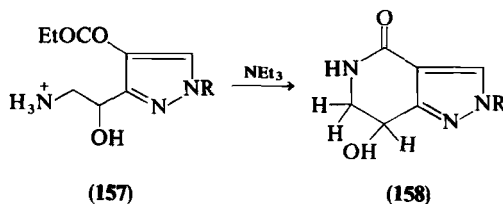
Heteroaromatic vinyl isocyanates have been used as a source of bicyclic pyridones. In the preparation of the 1-methylpyrazolo[4,3-*c*]pyridone **153** the isocyanate **152b**, obtained by Curtius rearrangement of the corresponding acid azide **152a**, was heated at 220°C in diphenyl ether to furnish the product in good yield.^{143,144} Several 2-alkyl derivatives were also prepared.¹⁴⁴

¹⁴² S. B. Barnela, R. S. Pandit, and S. Seshadri, *Indian J. Chem., Sect. B* **14B**, 665 (1976).

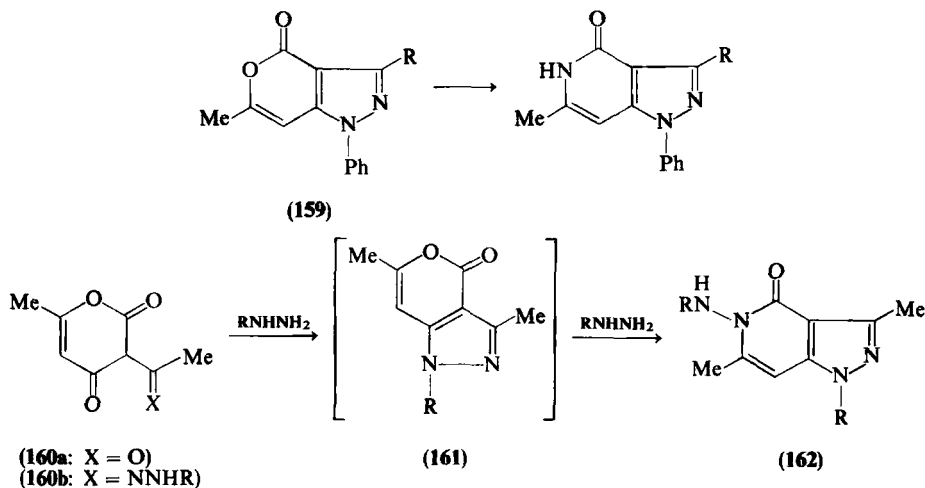
¹⁴³ F. Eloy and A. Deryckere, *J. Heterocycl. Chem.* **7**, 119 (1970).

¹⁴⁴ F. Eloy and A. Deryckere, *Chim. Ther.* **6**, 1 (1971).

b. *Reduced Pyrazolo[4,3-*c*]pyridines.* The aminoethylpyrazoles **157** ($R = \text{Me}, \text{CH}_2\text{Ph}$) cyclized, in the presence of base, to the reduced pyrazolo[4,3-*c*]pyridones **158**. These were thermally dehydrated to the 2-substituted derivatives.¹⁴⁶ The 1-substituted isomers were also prepared.



c. *Pyrazolopyrones.* Ammonia at high temperature and pressure converts the pyrazolopyrones **159** ($R = \text{Me}, 2\text{-furyl}$)^{134,141} to the corresponding pyridines. The formation of pyrazolo[4,3-*c*]pyridones **162** ($R = \text{Ar}, \text{CONH}_2$) via the hydrazones **160b** of acyl compound **160a** can be explained by invoking pyrazolopyrones **161** as intermediates.¹⁴⁷

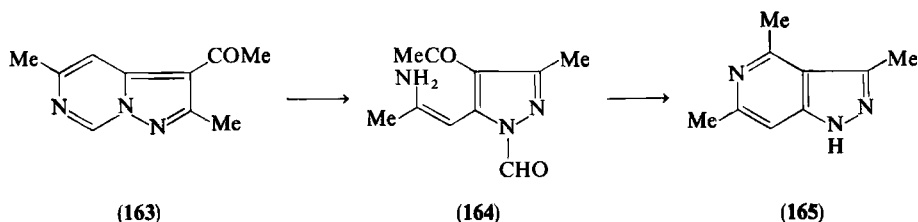


d. *Pyrazolopyrimidines.* Attempted deacetylation of pyrazolopyrimidine **163** resulted in hydrolytic fission of the N-6—C-7 bond, generating the aminovinylpyrazole **164** (see Section II,E,4). Subsequent ring closure and deformylation of **164** afforded a moderate yield of the trimethyl derivative **165**.¹⁴⁸

¹⁴⁶ J. D. Bourzat, J. P. Marquet, A. Grier, and E. Bisagni, *Tetrahedron* **29**, 441 (1973).

¹⁴⁷ V. K. Mahesh and R. S. Gupta, *Indian J. Chem.* **12**, 570 (1974).

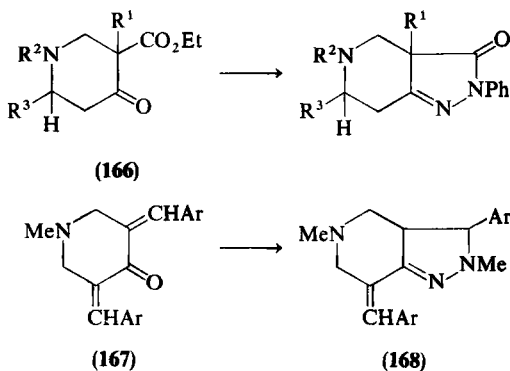
¹⁴⁸ K. H. Oehringen, D. Saffer, G. Sporidi, and H. Bretschneider, *Monatsh. Chem.* **92**, 313 (1961).



F. SYNTHESIS OF REDUCED PYRAZOLO[4,3-*c*]PYRIDINES

1. From 4-Piperidones

4-Piperidones containing suitable electrophilic substituents in the 3-position react with hydrazines to produce hexahydropyrazolo[4,3-*c*]pyridines. The potential for obtaining mixed isomers from unsymmetrical hydrazines has not been realized, 2-substituted derivatives being obtained in every case. For example, the 3-ethoxycarbonyl-4-piperidones **166** ($R^1 = H, Me, R^2 = Me, Ac, R^3 = H, Ph$)^{148,149} and phenylhydrazine gave the corresponding 2-phenyl products. Similarly, the diarylidenopiperidones **167** were converted to **168** on heating with methylhydrazine.¹⁵⁰ Numerous applications of the last reaction have been reported.^{151,152}



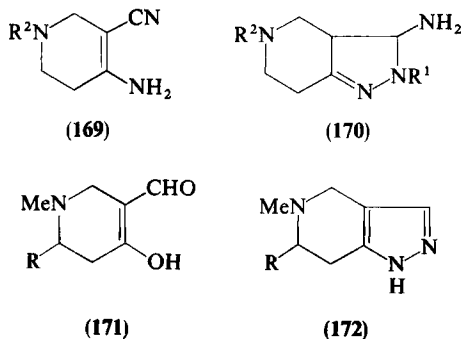
¹⁴⁹ K. G. Pfeffer, P. Brandt, A. Buege, H. J. Hahn, G. Heeger, and L. Reppel, *Pharmazie* **32**, 676 (1977).

¹⁵⁰ E. R. Squibb and Sons, Japanese Kokai 34,193 (1976) [*CA.* **87**, 152194 (1977)]; J. Krapcho and C. F. Turk, Fr. Demande 2,279,399 (1976) [*CA.* **86**, 16666 (1977)].

¹⁵¹ K. Krapcho and C. F. Turk, Ger. Offen. 2,430,590 (1975) [*CA.* **82**, 170918 (1975)]; U.S. Patent 3,926,968 (1975) [*CA.* **84**, 105586 (1976)]; U.S. Patent 3,931,169 (1975) [*CA.* **84**, 105588 (1976)].

¹⁵² J. Krapcho and C. F. Turk, Swiss Patent 594,667 (1978) [*CA.* **88**, 136616 (1978)]; U.S. Patent 4,065,617 (1977) [*CA.* **88**, 105328 (1978)].

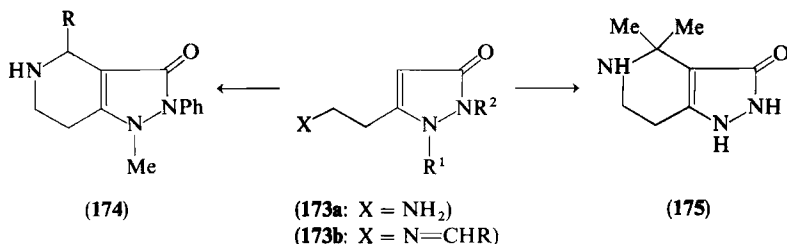
Several amino compounds (**170**: $R^1 = H, Me$; $R^2 = H, CH_2Ph$) were obtained from analogous reactions in which the 3-cyano-4-aminotetrahydropyridines (**169**) were treated with hydrazines.¹⁵³ Cyclization of the enols **171**, however, under similar conditions afforded the tetrahydro bicycles **172** ($R = H, Me$).^{154,155}



2. From Aminoethylpyrazoles

The formation of reduced pyrazolo[4,3-*c*]pyridones from aminoethylpyrazoles has been discussed (Section II,E,6,b).

In addition, condensation of pyrazolones **173a** with aldehydes and subsequent cyclization of the resultant imines **173b** gave the 4-substituted products **174** ($R = Me, Ph$).⁴⁶ Under basic conditions, however, acetone and **173a** cyclized spontaneously, giving the 4,4-dimethyl derivative **175**.¹⁵⁶



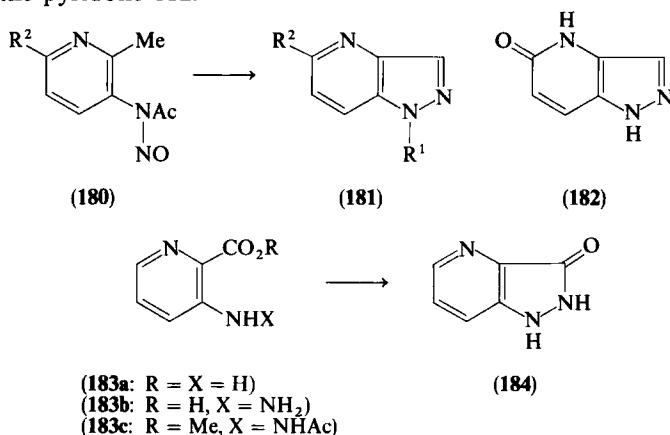
¹⁵³ K. Arimura and S. Murukami, Japanese Kokai 63,193 (1976) [*CA*, **86**, 5454 (1976)].

¹⁵⁴ L. H. Schlager, *Arch. Pharm. (Weinheim. Ger.)* **296**, 758 (1963).

¹⁵⁵ A. S. Norovyan, S. P. Mambreyan, and S. A. Vartunyan, *Arm. Khim. Zh.* **30**, 184 (1977) [*CA*, **87**, 68308 (1977)].

¹⁵⁶ J. Lykeberg, *Acta Chem. Scand., Ser. B* **332**, 56 (1978).

and a similar mechanism is proposed.¹⁵⁷ Acid hydrolysis of the products gave the corresponding 1-*H* derivative, except for **181** ($R^2 = \text{OMe}$), which yielded the pyridone **182**.



3. From Azo- and Hydrazinopyridines

The formation of mixtures of pyrazolo[3,4-*c*]- and -[4,3-*b*]pyridines from 3-phenylazopyridines has been discussed (Section II,C,4).

Acid-catalyzed cyclization of hydrazinopyridine **183b** afforded the pyrazolone **184**¹¹⁵ (cf. Section II,C,3). The acylhydrazinopyridine **183c** was similarly converted to **184**¹⁹ (cf. Section II,C,4).

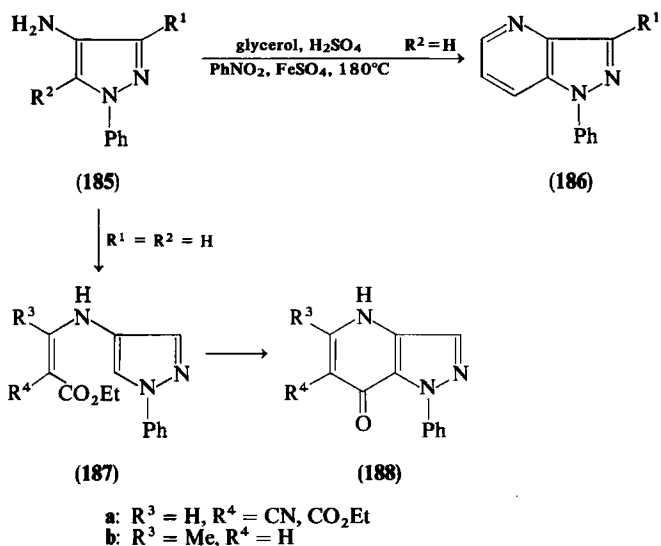
4. From 4-Aminopyrazoles

The Skraup reaction has been applied to the synthesis of pyrazolo[4,3-*b*]pyridines (cf. Section II,A,8) but is limited, because of the vigorous conditions involved, to the preparation of alkyl- or phenyl-substituted derivatives. Thus under Skraup conditions **185** ($R^2 = \text{H}$) furnished a moderate yield of 1-phenyl products (**186**, $R^1 = \text{H, Me}$),^{4,89} which were assigned, using UV spectroscopy.⁴ Attempts to form the 2-substituted isomer from the 5-substituted 4-aminopyrazole **185** ($R^1 = \text{H}$; $R^2 = \text{Me}$) were unsuccessful.⁴

Reaction of diethyl ethoxymethylenemalonate or ethyl cyanoethoxymethylene acetate with 1-phenyl-4-aminopyrazole gave esters **187a**, which cyclized in boiling Dowtherm to the corresponding pyridones **188a**.¹⁵⁸ The

¹⁵⁸ H. E. Foster and J. Hurst, *J. C. S. Perkin Trans. I*, 507 (1976).

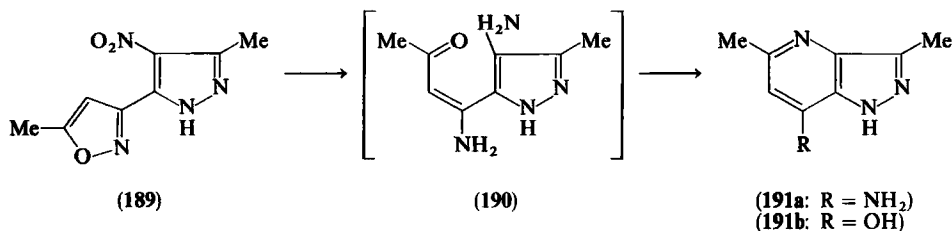
position of the phenyl substituent was deduced from the UV spectra. Attempts to induce cyclization of **187a** in polyphosphoric acid were unsuccessful, as were attempts to prepare a 2-substituted isomer.¹⁵⁸



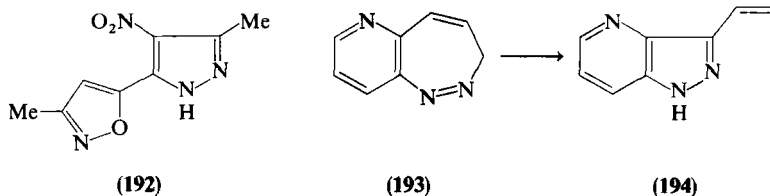
The use of ethyl acetoacetate gave the crotonate **187b**, which was similarly converted to pyridone **188b**,⁴⁹ which is in agreement with reports from the pyrazolo[3,4-*b*]pyridine series (Section II,A,6).

5. From Isoxazolylnitrosopyrazoles

Hydrogenation of isoxazole **189** over Raney nickel afforded the 7-amine **191a**, probably via the intermediate **190**. In addition, reduction of the isomeric isoxazole **192** effected formation of the pyridone **191b**.¹⁵⁹



¹⁵⁹ E. Ajello, *J. Heterocycl. Chem.* **8**, 1035 (1971).

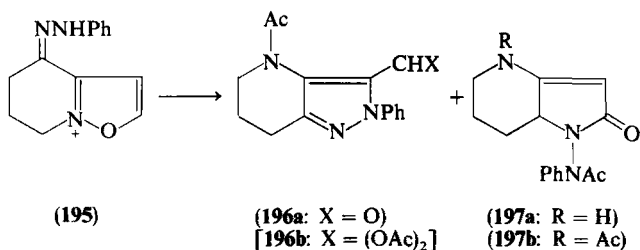


6. From Pyrido[2,3-*c*]diazepine

3-Vinylpyrazolo[4,3-*b*]pyridine (**194**) has been prepared in good yield by photochemical ring contraction of pyridodiazepine **193** in dichloromethane or methanol. The yield was improved by thermolysis of **193** in refluxing xylene⁹⁷ (cf. Section II,A,9,a).

H. SYNTHESIS OF REDUCED PYRAZOLO[4,3-*b*]PYRIDINES

The literature contains only one report describing reduced pyrazolo[4,3-*b*]pyridines. Refluxing the isoxazolium salt **195** in acetic anhydride for a short time gave a mixture of aldehyde **196a** and the reduced pyrrolopyridone **197a**. Extended reflux afforded diacetate **196b** together with **197b**.¹⁶⁰



I. SYNTHESIS OF PYRAZOLO[1,5-*a*]PYRIDINES

The chemistry used in the preparation of pyrazolo[1,5-*a*]pyridines is influenced by the presence of the bridgehead nitrogen. Syntheses involve the almost exclusive use of *N*-aminopyridinium salts and often require the generation of ylides.

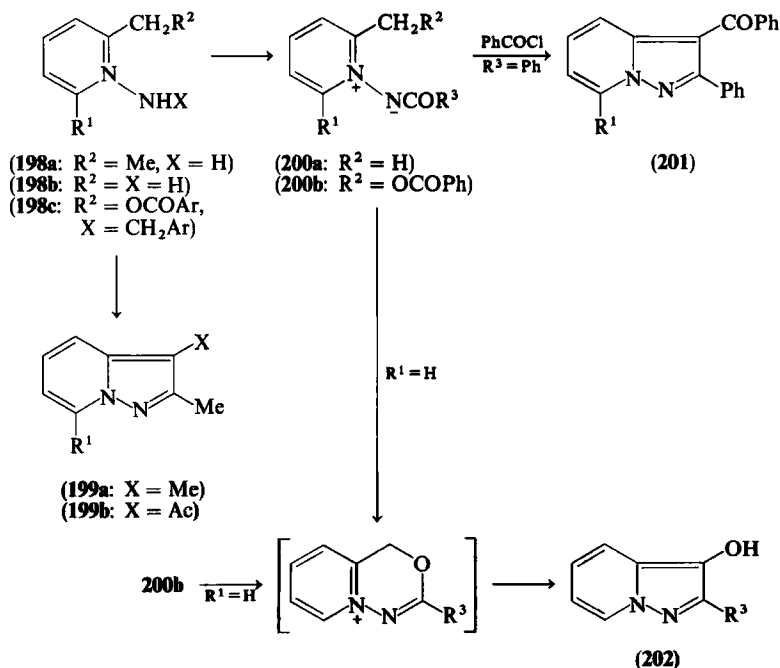
The *N*-aminopyridinium precursors can be divided into two major groups: (i) those containing a 2-methylene group, which cyclize on treatment with

¹⁶⁰ G. Jones, J. R. Phipps, and P. Rafferty, *Tetrahedron* **34**, 1581 (1978).

acylating agents, or (ii) those possessing no 2-substituent, which form the pyrazole ring with dipolarophiles.

1. From N-Aminopyridinium Salts Containing 2-Methylene Groups

Reaction of acetyl chloride with the 2-ethylpyridinium salt **198a** ($R^1 = H$) gave 2,3-dimethylpyrazolo[1,5-*a*]pyridine **199a**,¹⁶¹ whereas the 2-methyl analogs **198b** ($R^1 = H, Me$) afforded 3-acyl derivatives **199b**,^{161,162} both in low yield. Furthermore, products **199a** ($R^1 = Me$) and **199b** ($R^1 = Et$) were formed in approximately equal amounts from the dialkylpyridinium salt **198a** ($R^1 = Me$).¹⁶¹ The formation of acyl derivatives was attributed¹⁶¹ to the reactivity of the pyrazole ring (cf. Section III,A,4).



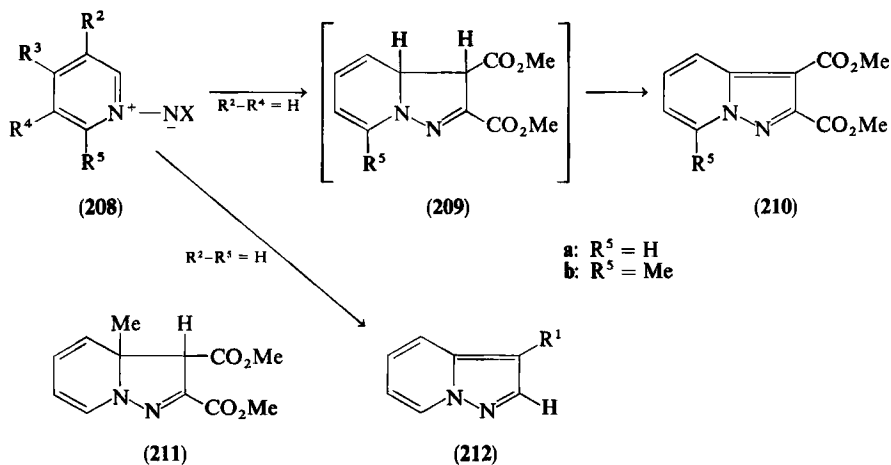
Addition of benzoyl chloride to **198a** produced the stable ylide **200a** ($R^3 = Ph$), which was converted to **201** ($R^1 = H, Me$) only on prolonged reflux. Suzue *et al.*¹⁶³ cyclized analogous ylides in the presence of iodine to afford

¹⁶¹ K. T. Potts, U. P. Singh, and J. Bhattacharya, *J. Org. Chem.* **33**, 3766 (1968).

¹⁶² T. Irikura, M. Hayashi, K. Koshirac, H. Urawa, and E. Hetsugi, Ger. Offen. 2,315,801 (1973) [*CA*, **80**, 14923 (1974)].

¹⁶³ S. Suzue, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* **21**, 2146 (1973).

products were obtained, using dibenzoylacetylene.¹⁷² Huisgen *et al.*¹⁶⁸ proposed formation of the dihydro intermediate **209**, and a number of cyclo-adducts were later prepared by Sasaki *et al.*¹⁷³ (Section II.I,2,b) who demonstrated their facile dehydrogenation. Further, a substituted dihydro derivative (**211**) was isolated in addition to **210b** from the cyclization of **208b** ($X = \text{CO}_2\text{Et}$).¹⁷¹



Treatment of ylides **208a** with methoxycarbonyl- or cyanoacetylene gave the corresponding 3-substituted isomers **212** ($R^1 = \text{Ac}, \text{CN}$).^{167,169,174,175} The effect of 3-substituents in the pyridine ring on the ratio of 4- to 6-substituted products has also been examined.¹⁷⁴

b. Vinyl Compounds. Chloro- or ethoxyvinyl compounds react with *N*-aminopyridinium salts to generate aminidines **213a** and **215**, which undergo thermal¹⁷⁶ or photochemical¹⁷³ cyclization to pyrazolo[1,5-a]pyridines **214** ($R^1 = H, \text{CO}_2\text{Et}$) in low yield. In contrast, thermolysis of the diacetyl analog **213b** resulted in *N*—*N* bond fission to give 4-acetyl-5-methyl isoxazole.¹⁷⁶ Milder treatment of ylide **215** afforded stable 3,3a-dihydro derivatives, which were oxidized to diesters **214** ($R^1 = \text{CO}_2\text{Et}$) in high yield.¹⁷³

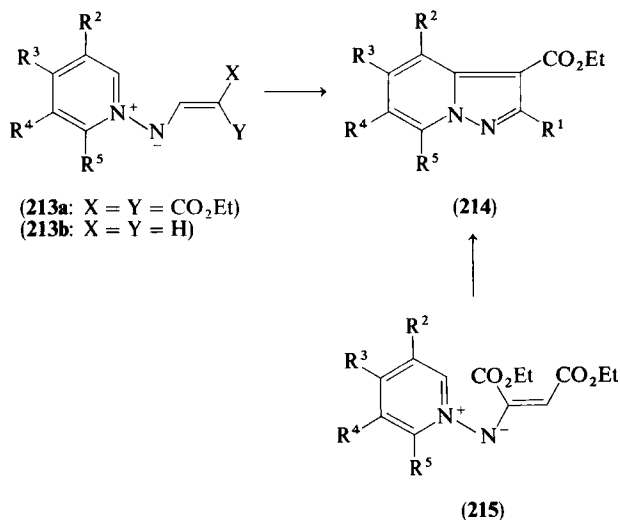
¹⁷² K. T. Potts, H. P. Youzwak, and S. J. Zurawel, *J. Org. Chem.* **45**, 90 (1980).

¹⁷³ T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.* **37**, 3106 (1972).

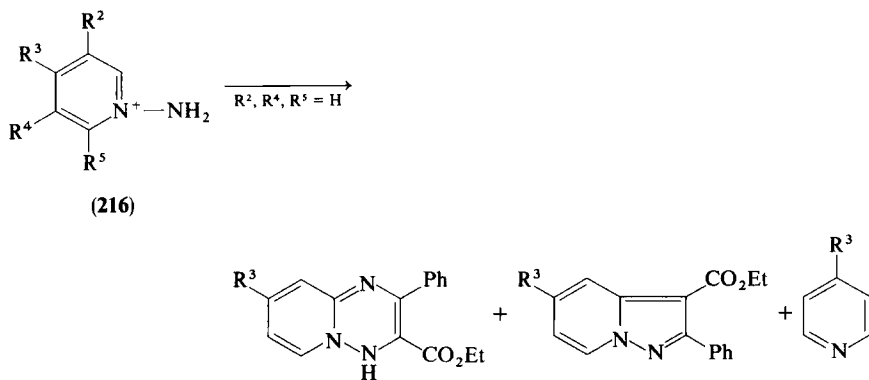
¹⁷⁴ Y. Tamura, Y. Miki, Y. Sumida, and M. Ikeda, *J. C. S. Perkin Trans. I*, 406 (1975).

¹⁷⁵ T. Sasaki, K. Kanematsu, and Y. Yakimoto, *J. Chem. Soc. C*, 481 (1970).

¹⁷⁶ Y. Tamura, Y. Miki, Y. Sumida, and M. Ikeda, *J. C. S. Perkin Trans. I*, 2580 (1973).



Addition of ethyl chlorocinnamate to **216** in the presence of base resulted in spontaneous cyclization to a mixture of products (Scheme 2). Ylides could not be detected during the reaction and an alternative mechanism was suggested.^{177,178} *In situ* generation of ylides **208** ($\text{R} = \text{H}$) in the presence of base and reaction with fluoro- and nitrovinyl compounds gave the corresponding 2,3-disubstituted products **217** ($\text{R} = \text{F}, \text{CF}_3$)¹⁷⁹ and **218**,¹⁸⁰ whereas methyl



SCHEME 2

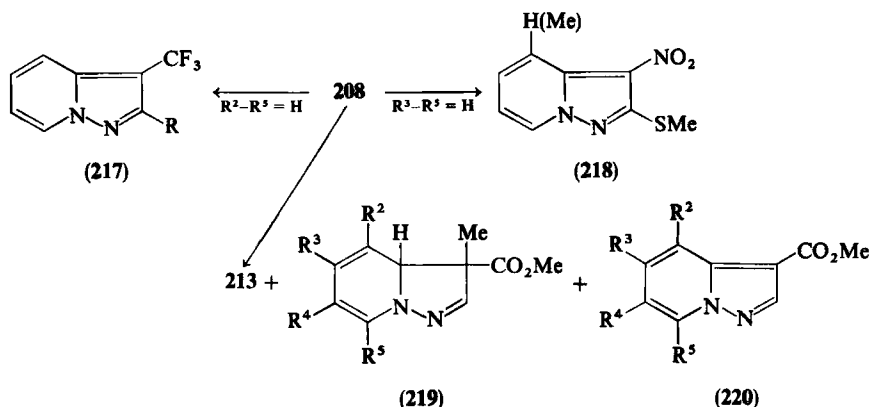
¹⁷⁷ A. Kakehi and S. Ito, *J. Org. Chem.* **39**, 1542 (1974).

¹⁷⁸ A. Kakehi, S. Ito, T. Manabe and E. Amans, *Hokusokan Kagaku Toronkai Koen Yoshishu*, 8th, 214 (1975) [*CA*, **84**, 164732 (1976)].

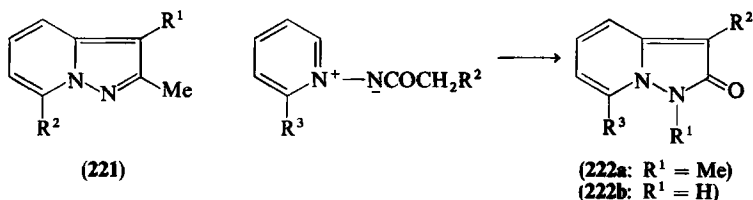
¹⁷⁹ R. E. Banks and S. M. Hitchen, *J. Fluorine Chem.* **15**, 179 (1980).

¹⁸⁰ H. Fujito, Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Heterocycles* **6**, 379 (1977).

3-bromomethacrylate furnished additional products (**213**, **219**, and **220**).¹⁸¹ The dihydro compounds **219** were readily aromatized to **220** but, surprisingly, the ylides **213** ($X = \text{Me}$, $Y = \text{CO}_2\text{Me}$) could not be cyclized, suggesting formation of bicyclic products by 1,3-dipolar cycloaddition.



c. Active Methylene Groups. *N*-Aminopyridinium salts and acetylacetone or ethyl acetoacetate in the presence of base at 80°C furnished the compounds **221** ($R^1 = \text{Ac}$, CO_2Et , $R^2 = \text{H}$, Me)^{162,182} in good yield. Other workers carried out similar reactions at lower temperatures and isolated ylides, which were cyclized, with or without prior methylation, to the pyrazolones **222a** and **222b**.^{183,184} The formation of dihydro intermediates was proposed.¹⁸³ The introduction of a 2-thiomethyl substituent into the pyridine ring generally improved the yields of product. On treatment with nitriles, a number of salts (**223**: $R^5 = \text{NH}_2$, Ph)^{185,186} cyclized by displacement of the thiomethyl function to afford the amines **224a**. The use of



¹⁸¹ T. Sasaki, K. Kanematsu, and A. Kakehi, *Tetrahedron Lett.*, 5245 (1972).

¹⁸² Y. Tamura, A. Yamakami, and M. Ikeda, *Yakugaku Zasshi* **91**, 1154 (1971) [*CA*, **76**, 34164 (1971)].

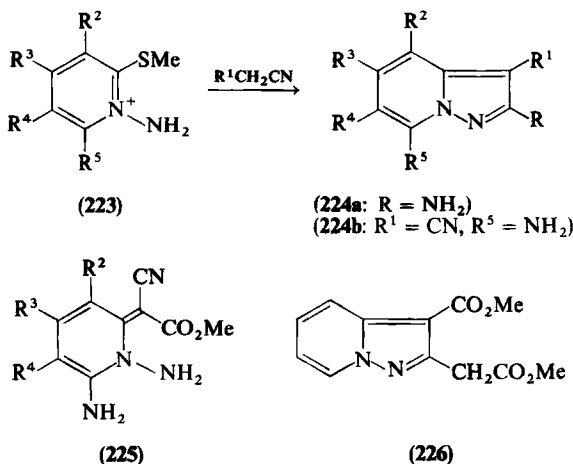
¹⁸³ A. Kakehi, S. Ito, Y. Konno, and T. Maeda, *Bull. Chem. Soc. Jpn.* **51**, 258 (1978).

¹⁸⁴ T. Kato and S. Masuda, *Chem. Pharm. Bull.* **23**, 452 (1975).

¹⁸⁵ K. Gewald, A. Schubert, and G. Martin, *J. Prakt. Chem.* **317**, 561 (1975).

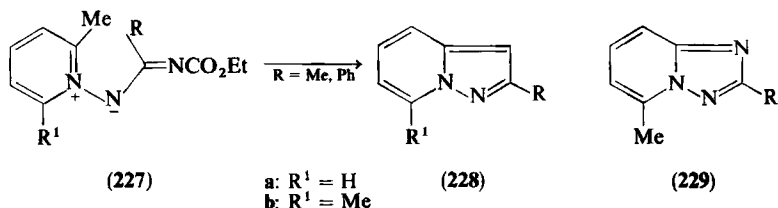
¹⁸⁶ A. Arques, H. Hernandez, P. Molina, and M. J. Vilaplana, *Synthesis*, 910 (1981).

benzoylacrylonitrile gave the corresponding amine as a by-product, together with the 3-cyano compound **224b** ($R = \text{Ph}$). A similar product (**224b**: $R = \text{OH}$) was obtained from **223**, ($R^5 = \text{NH}_2$) and methyl cyanoacetate via the isolated intermediate **225**.¹⁸⁵



d. *Dienes* The parent ylide, generated *in situ*, was treated with diethyl penta-2,3-dienedioate to afford the diester **226**.¹⁸⁷

e. *Imidates*. Stable ylides **227**, generated from **198b** and imidates, were thermolyzed in xylene to furnish a variety of products. The pyrazole ring was formed only when the starting material contained an *o*-methyl group. For example, **227a** gave mixtures of **228a** and the triazoles **229**, whereas dimethyl-substituted precursors **227b** afforded **228b** only.¹⁸⁸

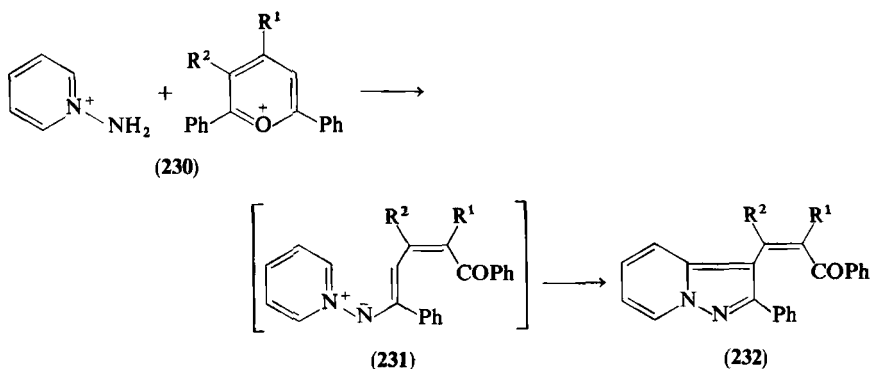


f. *Pyrylium Salts*. Nucleophilic attack at C-2 in the pyrylium ring **230** generates the proposed ylide intermediates **231** (cf. Section II,I,2,b), which

¹⁸⁷ R. M. Acheson, M. G. Bite, and M. W. Cooper, *J. C. S. Perkin Trans. 1*, 1908 (1976).

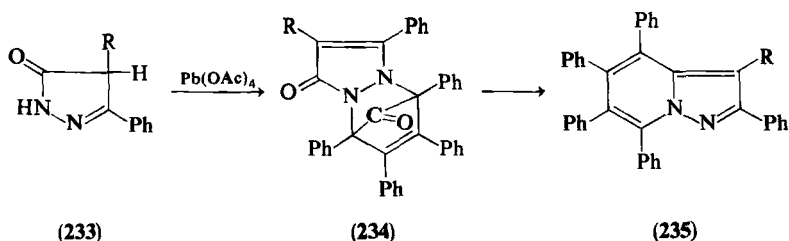
¹⁸⁸ A. Kakehi, S. Ito, K. Uchiyama, Y. Konno, and K. Kondo, *J. Org. Chem.* **42**, 443 (1977).

gave a moderate yield of the 2-phenyl-3-vinyl derivatives **232**, possibly via a dihydro compound.¹⁸⁹



3. From Pyrazole Derivatives

a. *5-Pyrazolines*. Oxidation of pyrazolinones **233** in the presence of tetraphenylcyclopentadienone (TPCD) gave the Diels–Alder adduct **234** of the unstable pyrazolone. Thermolysis of **234** eliminated carbon dioxide, forming the pentaphenyl derivative **235** ($\text{R} = \text{Ph}, \text{H}, \text{CH}_2\text{Ph}$) together with TPCD as a retro Diels–Alder product.^{190,191}



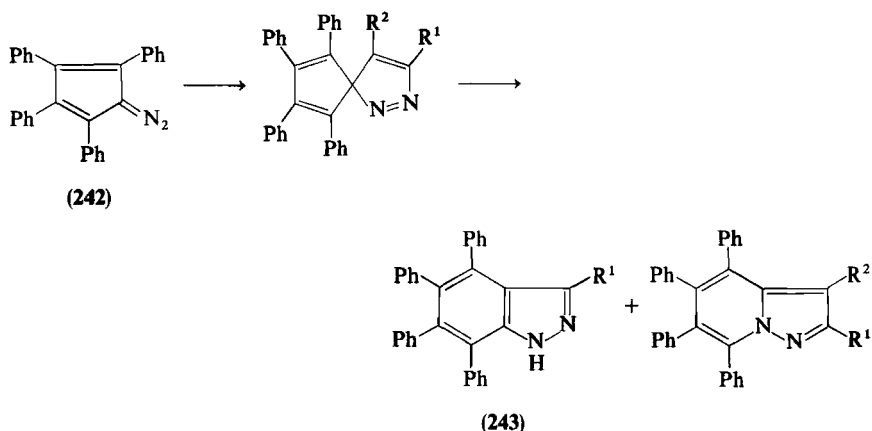
b. *Cyanomethylpyrazoles*. The conversion of *N*-substituted cyanomethylpyrazoles to pyrazolo[4,3-*c*]pyridines has been discussed (Section II,E,3). When the pyrazole does not carry an *N*-1 substituent, an alternative direction of cyclization is available. Treatment of **236** with ethyl acetoacetate afforded a pyrazolo[1,5-*a*]pyridine (**237a**), the structure of which was not fully established. Condensation with acetylacetone gave a mixture of the

¹⁸⁹ T. Toda, H. Morino, Y. Suzuki, and T. Mukai, *Chem. Lett.*, 155 (1977).

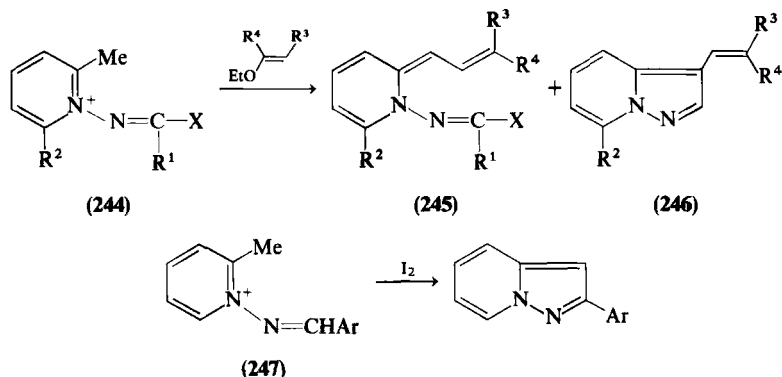
¹⁹⁰ C. W. Rees and M. Yelland, *J. Chem. Soc. D*, 377 (1969).

¹⁹¹ C. W. Rees and M. Yelland, *J. C. S. Perkin Trans. I*, 221 (1973).

indazoles **243**.¹⁹⁴⁻¹⁹⁶ In the presence of an acid catalyst **243** were the sole products.^{195,196}



d. *From 2-Methylpyridines.* 2-Methylpyridinium salts **244** [$X = \text{SMe}$, $\text{N(Me)CO}_2\text{Et}$] reacted with vinyl ethers at room temperature to yield mixtures of 3-vinyl derivatives **246** and allylidenedihydropyridines **245**. The latter compounds were readily converted to **246** in refluxing xylene or benzene. The introduction of an additional *o*-methyl group favored the direct formation of the bicycle.¹⁹⁷⁻²⁰¹



¹⁹⁴ H. Duerr and R. Sergio, *Tetrahedron Lett.*, 3479 (1972).

¹⁹⁵ H. Duerr and R. Sergio, *Chem. Ber.* **107**, 2027 (1974).

¹⁹⁶ H. Duerr and W. Schmidt, *Liebigs Ann. Chem.*, 1140 (1974).

¹⁹⁷ A. Kakehi, S. Ito, K. Uchiyama, and K. Kondo, *Chem. Lett.*, 545 (1977).

¹⁹⁸ A. Kakehi, S. Ito, K. Uchiyama, and K. Kondo, *J. Org. Chem.* **43**, 2896 (1978).

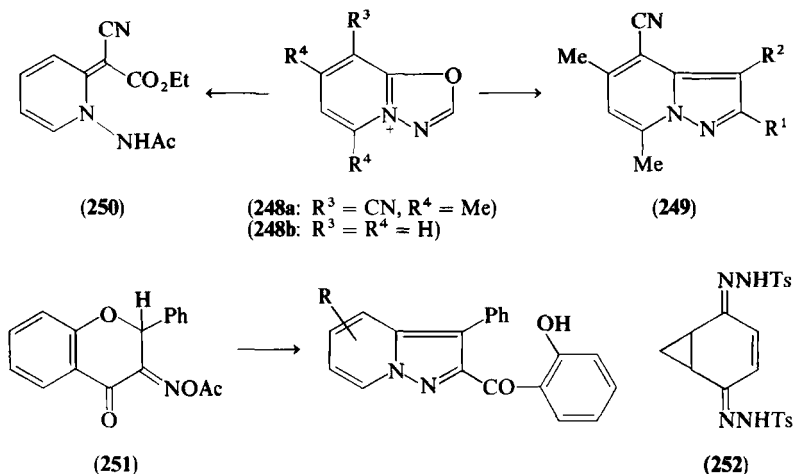
¹⁹⁹ A. Kakehi, S. Ito, K. Watanabe, T. Ono, and T. Miyazima, *Chem. Lett.*, 205 (1979).

²⁰⁰ A. Kakehi, S. Ito, K. Watanabe, T. Ono, and T. Miyazima, *J. Chem. Res., Synop.*, 18 (1980).

²⁰¹ A. Kakehi, S. Ito, and K. Watanabe, *Bull. Chem. Soc. Jpn.* **53**, 1775 (1980).

A number of 2-aryl derivatives were obtained by oxidation of the 2-methylpyridinium salts **247** in refluxing pyridine.²⁰²

e. *From Oxadiazolopyridinium Salts.* Active methylene compounds cleaved the five-membered ring in oxadiazolium salt **248a**, giving 2,3-disubstituted pyrazolo[1,5-*a*]pyridines **249**. The unsubstituted bicycle **248b** reacted in an analogous fashion with ethyl acetoacetate but with the cyanoester gave dihydropyridine **250**, which could not be cyclized.²⁰³



f. *From Isonitrosoflavanones.* Refluxing the nitrosoacetate **251** with simple pyridines resulted in solvolysis to the 2-aryl derivatives. Formation of a tetracyclic intermediate was tentatively suggested.²⁰⁴

g. *From homo-p-Quinone.* The parent pyrazolo[1,5-*a*]pyridine (**5**) has been obtained in moderate yield by thermolysis of *homo-p*-quinone **252** in diglyme. A mechanism involving acyclic ylides has been proposed.²⁰⁵

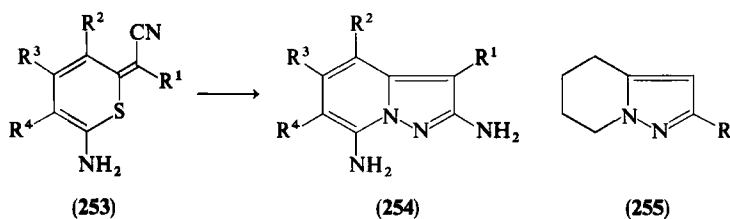
h. *From Thiopyrans.* A number of thiopyrans (**253**) on treatment with hydrazine cyclize with expulsion of hydrogen sulfide to form the 2,7-diamino derivatives **254** ($R^1 = \text{CN}, \text{CO}_2\text{Et}, \text{CONH}_2$).¹⁸⁵

²⁰² T. Okamoto, M. Hirobe, S. Suzue, Y. Nagatsu, K. Ushiyama, S. Sato, and T. Irikura, *Ger. Offen.* 2,118,917 (1972) [*CA.* 77, 19641 (1972)].

²⁰³ G. V. Boyd and S. R. Dando, *J. Chem. Soc. C*, 225 (1971).

²⁰⁴ M. Michalska, *Tetrahedron Lett.*, 2667 (1971).

²⁰⁵ C. B. Chapleo and A. S. Dreiding, *Helv. Chim. Acta* 57, 1259 (1974).



J. SYNTHESIS OF REDUCED PYRAZOLO[1,5-a]PYRIDINES

1. From Pyrazolo[1,5-a]pyridines

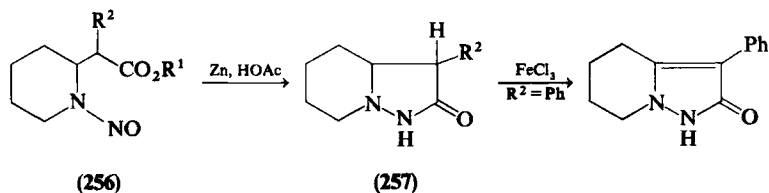
Sodium-liquid ammonia reduction of the parent bicycle gave a smooth conversion to the 4,5,6,7-tetrahydro derivative **255** (R = H).¹⁶⁵ Reduction of the pyridine ring to give **255** was also observed during hydrogenation of 2-hydroxypyrazolo[1,5-a]pyridine (**240**; R = OH) over platinum oxide.¹⁹²

2. From Aminopyridinium Ylides

Several ylides (**208**; X = aryl, heteroaryl) on treatment with acrylonitrile cyclized to the tetrahydro derivatives.^{206,207}

3. From Piperidineacetic Acid Derivatives

Reductive cyclization of *N*-nitrosopiperidineacetic acid (**256**; R¹ = H, Me, R² = Ph)^{208,209} afforded saturated bicycles **257** possibly via *N*-amino-piperidine intermediates. Partial oxidation or dehydration of the products could be accomplished.



²⁰⁶ H. Beyer, K. Leverenz, and H. Schilling, *Angew. Chem.*, **73**, 272 (1961).

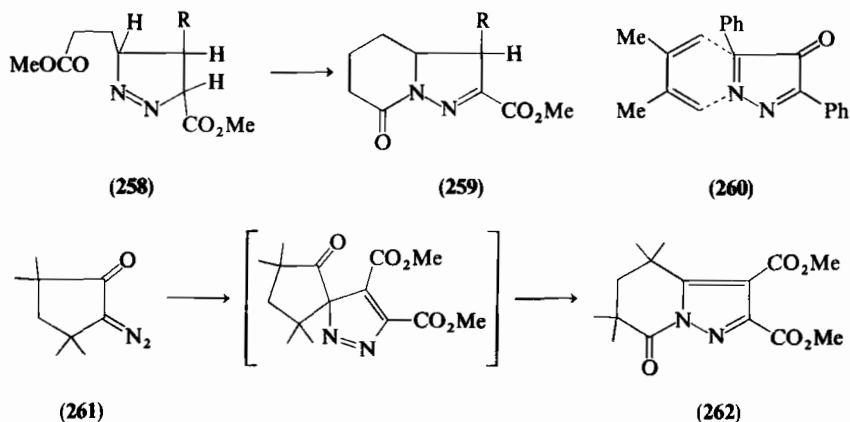
²⁰⁷ H. Beyer and E. Thieme, *J. Prakt. Chem.* **21**, 293 (1966).

²⁰⁸ G. Destevens and M. Dernier, *J. Med. Chem.* **7**, 146 (1964).

²⁰⁹ E. E. Mikhlin, N. A. Komarova, and M. V. Rubstov, *Chem. Heterocycl. Compd. (Engl. Transl.)* **5**, 629 (1969).

4. From Pyrazoles

Pyrolysis of the pyrazoline butanoic acid esters **258** gave the lactams **259** ($R = H, CO_2Et$).²¹⁰ Pyrazolone **260** reacted with 2,3-dimethyl-1,3-butadiene to furnish the expected cycloadduct.²¹¹



5. From Diazocyclopentanones

The formation of pyrazolo[1,5-*a*]pyridines from diazocyclopentadienes was discussed in Section II, I, 4, c. The cyclopentanone **261** was converted to the corresponding reduced product **262** upon treatment with dipolarophiles, possibly involving [1,5]-sigmatropic rearrangement of the intermediate spiro adduct.²¹²

III. Chemical Reactions

The reactions of pyrazolopyridines have not been studied in detail; nevertheless, sufficient information is available to demonstrate similarities between the five isomers.

²¹⁰ S. Hauptmann and K. Hirshberg, *J. Prakt. Chem.* **36**, 73 (1967).

²¹¹ P. J. Fagan, E. E. Neidert, M. J. Nye, M. J. O'Hare, and W. P. Tang, *Can. J. Chem.* **57**, 904 (1979).

²¹² L. L. Rodina, V. V. Bulusheva, and I. K. Korobitsyna, *J. Org. Chem. USSR (Engl. Transl.)* **10**, 1948 (1974).

MO calculations for **5**^{192,213–216} and **1**²¹⁷ and their conjugate acids indicate high π -electron density at position 3; in common with pyrrolopyridines,⁷ this is found to be the predominant position for electrophilic substitution.

No example of nucleophilic substitution of hydrogen has been reported, but chloro and ethoxy groups are labile when conjugated with the azomethine moiety.

A. REACTION AT CARBON

1. Halogenation

Halogenation of pyrazolo[4,3-*c*]pyridines has not been reported, but all other isomers, as with pyrrolopyridines, undergo substitution mainly in the 3-position.

Halogenation of pyrazolo[1,5-*a*]pyridine (**5**) with aqueous bromine,²¹³ methanolic bromine in the presence of sodium acetate,¹⁹² or KI–I₂¹⁹² gave the 3-substituted products (80, 60, and 63%, respectively). One equivalent of bromine in glacial acetic acid converted the 2-hydroxy derivative **240** (R = OH) to the corresponding 3-bromo compound (56%), whereas excess bromine afforded a 1,3-disubstituted product (60%) as evidenced by IR and NMR spectrometry.¹⁶⁶ Bromine water at room temperature was used in the preparation of 3-bromopyrazolo[3,4-*c*]- (60%),¹¹⁰ 3-bromo-5-methylpyrazolo[4,3-*b*]- (97%),¹¹¹ and 3-bromo-5-hydroxypyrazolo[4,3-*b*]pyridines (63%).¹¹¹ At higher temperature the last compound was converted to a 3,6-dibromo derivative (54%).¹¹¹ 1-Benzyl-3-bromopyrazolo[3,4-*b*]pyridine was obtained in low yield using *N*-bromosuccinimide and the 3-chloro analog, using chlorine in carbon tetrachloride.⁸⁸ 3-Chlorination of pyrazolo[3,4-*c*]pyridine (**2**) was achieved (40%), using sodium hypochlorite.¹¹⁰

Japanese workers²¹⁸ report the formation of 2-alkyl-3-halopyrazolo[1,5-*a*]pyridines from the corresponding 3-acyl derivatives, whereas attempted perchlorination of **5** with phosphorus pentachloride in a steel bomb gave a 48% yield of perchloropyridine.²¹⁹

²¹³ W. N. Paudler and D. E. Dunham, *J. Heterocycl. Chem.* **2**, 410 (1965).

²¹⁴ B. M. Lynch and B. P. L. Lem, *J. Heterocycl. Chem.* **11**, 223 (1974).

²¹⁵ E. Kleinpeter, R. Bordsdorf, G. Fischer, and H. J. Hoffmann, *J. Prakt. Chem.* **314**, 515 (1972).

²¹⁶ M. Witanowski, L. Stefaniak, W. Sicinska, and G. A. Webb, *J. Mol. Struct.* **64**, 15 (1980).

²¹⁷ B. M. Lynch, A. J. Robertson, and J. G. K. Webb, *Can. J. Chem.* **47**, 1129 (1969).

²¹⁸ T. Okamoto, M. Hirobe, Y. Minamoto, and T. Irikura, Japanese Kokai, 11,399 (1975) [*CA*, **83**, 193305 (1975)].

²¹⁹ M. F. Depompei and W. N. Paudler, *J. Heterocycl. Chem.* **13**, 139 (1976).

2. Nitrosation

Nitrosation of parent,²¹⁴ 2-substituted^{166,202} or 4,5,6,7-substituted pyrazolo[1,5-*a*]pyridines²²⁰ occurred in the 3-position. Formation of 2-alkyl-3-nitroso analogs was also achieved by displacement of a 3-acyl group.²¹⁸

3. Nitration

3-Nitropyrazolo[1,5-*a*]pyridines^{166,214} were formed in good yield under mild conditions (mixed acids or fuming nitric acid at 0°C). At higher temperatures a 3,6-dinitro²¹⁴ and not a 3-nitro derivative, as previously suggested,¹⁹² was obtained. Oxidation of a 3-nitroso²¹⁴ or replacement of a 3-acyl substituent²¹⁸ has provided analogous products. Mixed acids at 120°C led to 3,6-dinitropyrazolo[4,3-*b*]pyrid-5-one, under which conditions only 3-nitro derivatives were obtained from parent and 5-methylpyrazolo[3,4-*c*]-¹¹⁰ or 5-methylpyrazolo[4,3-*b*]pyridines.¹¹¹ The activating effect of a pyridone structure has also been observed in the 7-nitration of pyrazolo[4,3-*c*]pyridone **153**.¹⁴⁴ Nitration of parent (**1**) or 1-methylpyrazolo[3,4-*b*]pyridines is claimed to produce 3-nitro compounds,⁷⁹ whereas the 1-benzyl analog and its 7-oxide afforded only phenyl-substituted products.⁸⁸

4. Acylation

Acylation¹⁶¹ of pyrazolo[1,5-*a*]pyridines during the attempted syntheses of 3-*H* derivatives has been discussed (Section II,I,1). In addition, 3-acyl²²¹ and 3-benzoyl analogs¹⁹² have been obtained by refluxing the bicycle in the appropriate acyl chloride.

5. Miscellaneous

A 3-sulfonic acid was obtained from reaction of oleum with pyrazolo[1,5-*a*]pyridine.¹⁹²

A benzenediazonium salt in pyridine coupled with 2,3-diphenylpyrazolo[4,3-*c*]pyridin-4,6-dione in the 7-position.¹⁴⁰ Similar treatment of 1,3-disubstituted pyrazolo[3,4-*b*]pyrid-4-ones afforded the 5-arylazo products.²²²

²²⁰ T. Okamoto, T. Irikura, S. Suzue, K. Ushiyama, Y. Matsui, Y. Nagatsu, S. Sato, H. Yokoyama, and K. Saito, Japanese Kokai 72,193 (1973) [*CA*. **80**, 37105 (1974)].

²²¹ T. Irikura, Ger. Offen. 2,546,196 (1976) [*CA*. **85**, 63063 (1976)].

²²² Sandoz Ltd., Belgian Patent 658,588 (1965) [*CA*. **64**, 6791 (1966)].

B. REACTION AT NITROGEN

1. Acylation

Calculations on **1**²¹⁷ show the electron density on the nitrogen atoms to be lower than for indoles or pyrrolopyridines. Acylation, however, still proceeds under relatively mild conditions.

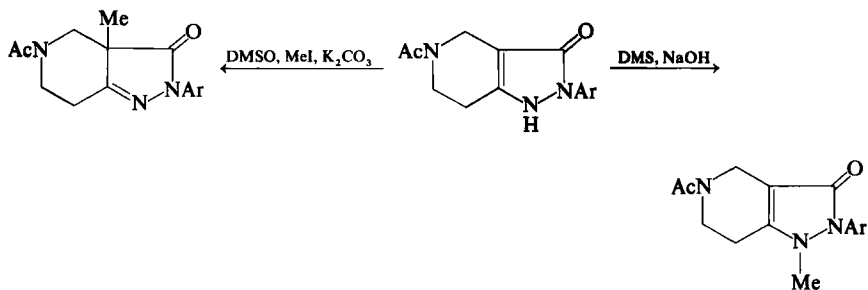
The acylation of a series of pyrazolo[3,4-*c*]pyridines has been studied.¹¹⁰ Acetic anhydride in refluxing benzene converted 5-substituted derivatives to 1-acyl compounds (**101**: $R^2 = H$), whereas the 7-methoxy derivative afforded the 2-substituted product **102** ($R^1 = H, R^2 = OMe$), attributed to *peri* interaction. In the absence of solvent, however, the latter reaction gave the 1-acyl isomer as the major product. Furthermore, benzylation of the 5-chloro bicycle furnished a mixture of **101** and **102** ($R^1 = Cl, R^2 = H$). However, products benzyolated mainly at N-6 were obtained following introduction of a nitro group into the pyrazole ring.

Pyrazolo[4,3-*b*]pyridine **181** ($R^1 = H, R^2 = Me$) in refluxing pyridine was acylated and tosylated in the 1-position. Milder conditions afforded either a 2-acyl or a mixture of 1- and 2-aroyl derivatives, suggesting a possible equilibrium between the two products.¹¹¹

Ridi *et al.*³⁸ report 1,2-diacetylation of pyrazolo[3,4-*b*]pyridone **29b** with acetic anhydride, which contrasts with the O-acetylation observed for similar systems (Section III,B,6).

2. Alkylation

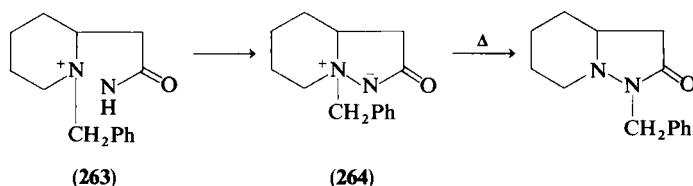
A mixture of 1- and 2-alkylated products was obtained from reaction of 5-methylpyrazolo[4,3-*b*]pyridine with methyl iodide in ethanolic sodium hydroxide.¹¹¹ Methylation of reduced pyrazolo[4,3-*c*]pyrid-3-ones gave either 1- or 3a-substituted products (Scheme 3).¹⁴⁹



SCHEME 3

3. Quaternization

Pyrazolo[4,3-*c*]pyridines gave 5-methiodides in excellent yield.^{144,154} A methiodide of pyrazolo[1,5-*a*]pyridine **199b** ($R^1 = H$) was also prepared but its structure was not assigned¹⁶¹; the parent compound **5** quaternized in the 1-position.²⁰⁹ The saturated amide, however, formed a 7*a*-quaternary salt (**263**) with benzyl chloride, which was converted to the 1-benzyl derivative via the internal salt **264**.²⁰⁹



4. Amination

Pyrazolo[3,4-*c*]- and 5-methylpyrazolo[4,3-*b*]pyridines were treated with hydroxylamino-*O*-sulfonic acid in ethanolic sodium hydroxide to furnish 1-amino or a mixture of 1- (42%) and 2-substituted products (40%), respectively, which were assigned on the basis of their UV spectra. Pyrazolo[3,4-*b*]pyridine (**1**), however, gave only water-soluble products, presumed to result from reaction at N-7.¹⁵⁷

5. Dealkylation

In the pyrazolo[3,4-*b*]pyridine series, the removal of a 1-furylmethyl group, using SeO_2 ^{86,223-225} or H_3PO_4 ,⁸⁴ is well documented. Debenzylation, however, met with mixed success. A number of 6-pyridones (erroneously assigned in the original papers) were dealkylated, using Na-NH_3 ^{50,74} or $\text{H}_2\text{-Pd-C}$.⁵² 1-Benzylpyrazolo[3,4-*b*]pyridine was resistant to a variety of reagents.⁸⁸ In contrast, both pyrazolo[4,3-*c*]pyridines and -pyridones have been debenzylated in moderate yield.^{144,146}

The removal of a 2-pyrimidyl substituent from derivatives of **1** occurred under mild conditions.⁶⁸

²²³ H. Hoehn and M. Chasin, Ger. Offen. 2,258,687 (1973) [*CA*. **79**, 92216 (1973)].

²²⁴ T. Denzel, Canadian Patent 1,003,419 (1977) [*CA*. **87**, 5963 (1977)].

²²⁵ T. Denzel and H. Hoehn, British Patent 1,460,059 (1977) [*CA*. **87**, 39477 (1977)].

6. *O*- versus *N*-Substitution

Substitution products of both tautomers have been reported for pyrazolopyridines containing the lactam moiety. Acetylation of **240** ($R = OH$) gave the acetoxy derivative, whereas diazomethane afforded the corresponding ether. Dimethyl sulfate, however, led to a 4:1 mixture of *O*- and *N*-methylated products.¹⁶⁶ The reaction of 3-hydroxypyrazolo[3,4-*b*]pyridines **21** with acetic anhydride³² or compounds containing the chloro- or epoxyalkyl moiety^{17,226} afforded only *O*-substituted products. A number of 4-alkoxy analogs have also been reported.^{80,87,227-230} In addition, 3-methyl-7-ethoxycarbonylpyrazolo[4,3-*c*]pyrid-4-one and ethyl iodide in the presence of base gave the corresponding ether.¹³⁴ Under more vigorous conditions, however, a 2-methylpyrazolo[3,4-*b*]pyrid-4-one gave the *N*-7-ethyl derivative.²³¹ Analogous products were obtained from pyrazolo[3,4-*b*]pyrid-6-⁶⁵ and -[4,3-*b*]pyrid-7-ones.¹⁵⁸ Further, quantitative benzylation of pyrazolo[4,3-*c*]pyridone **153** occurred at *N*-5 in sodium ethoxide.¹⁴⁴

C. REACTION OF FUNCTIONAL GROUPS

1. *Hydroxy*

The alkylation of hydroxy derivatives has been discussed (Section III,B,6). A major conversion of pyrazolopyridones has been to the labile chloro compounds, using phosphorus oxychloride, with addition of phosphorus pentachloride in some instances.^{34,115,146,159,166} Hydroxy groups in the pyrazole ring are relatively unreactive; for example, 2-chloropyrazolo[1,5-*a*]pyridine (72%)¹⁶⁶ and 3,6-dichloro-4-phenylpyrazolo[3,4-*b*]pyridine (7%)³⁴ were formed only at high temperature in a sealed tube. Under milder conditions it was possible to form the 6-chloro analog (9%) of the latter compound.³⁴ Vigorous conditions were also required for the formation of 4,6-dichloropyrazolo[4,3-*c*]pyridines,¹³⁹ although other workers^{134,144,146} have pre-

²²⁶ L. Kuczynski, A. Mrozikiewicz, and K. Poreba, *Pol. J. Pharmacol. Pharm.* **33**, 107 (1981); Polish Patent 106,897 (1980) [*CA.* **93**, 239427 (1980)]; Polish Patent 106,896 (1980) [*CA.* **93**, 239428 (1980)].

²²⁷ H. Hoehn, U.S. Patent 4,260,614 (1981) [*CA.* **95**, 62197 (1981)].

²²⁸ T. Denzel and H. Hoehn, Ger. Offen. 2,261,444 (1973) [*CA.* **79**, 92211 (1973)].

²²⁹ H. Hoehn and M. Chasin, Ger. Offen. 2,028,869 (1970) [*CA.* **74**, 76412 (1971)].

²³⁰ H. Hoehn and T. Denzel, Ger. Offen. 2,123,318 (1971) [*CA.* **76**, 59619 (1972)].

²³¹ T. Denzel and H. Hoehn, U.S. Patent 4,038,281 (1977) [*CA.* **87**, 168028 (1977)].

pared 4-chloro analogs (65–85%) by short reflux in phosphorus oxychloride. In addition, 5-^{111,115} and 7-chloropyrazolo[4,3-*b*]-,¹⁵⁹ 5-chloropyrazolo[3,4-*c*]-,¹¹⁵ and 4-^{46,82,85,87,230,232–234} and 6-chloropyrazolo[3,4-*b*]pyridines^{34,46,52,68} were formed from the corresponding pyridones under mild conditions. The 6-chloro derivatives (**81**: R¹ = Me, R² = H) were obtained by fusion of the lactams with phosphorus pentachloride.⁹⁵

Replacement of a hydroxy with a thiol group, using phosphorus pentasulfide in refluxing pyridine, has been reported for pyrazolo[4,3-*c*]pyrid-4-(54–75%)^{144,146} and pyrazolo[3,4-*c*]pyrid-7-ones (67%).¹¹⁰

2. Chloro

Nucleophilic substitution of hydrogen in the pyrazolopyridine system has not been reported. Replacement of a chlorine atom, however, is well known. No example of substitution in the pyrazole ring has been observed, and in the pyridine ring, chloro substituents are only active if conjugated with the azomethine moiety. Thus in the pyrazolo[3,4-*c*]pyridine ring a 5-chloro is inactive and a 7-chloro active toward nucleophiles. This was also reflected in the ease of hydrolysis of the corresponding methoxy derivatives.¹¹⁰ Likewise, in aminolysis of 4,6-dichloropyrazolo[4,3-*c*]pyridine the 6-chloro was resistant to attack.¹³⁹ Reactions of 4-chloro analogs with amines¹⁴⁴ or thiols^{144,146} have also been reported. A large number of 4-substituted pyrazolo[3,4-*b*]pyridines were thus produced from 4-chloro or 4-ethoxy derivatives. Compounds prepared include amines,^{100,134,228–230,233d,234,235} thiols,^{233a,b,e} and hydrazines.^{85,229} Further, a 6-hydrazino derivative⁶⁸ and several 7-ethoxy-¹⁵⁸ or 5-hydrazinopyrazolo[4,3-*b*]pyridines¹¹¹ were similarly prepared.

Hydrolysis of 6-chloropyrazolo[3,4-*b*]pyridine (**81**: R¹ = Me, R² = CHO) gave the corresponding pyridone.⁹⁵

Hydrogenation over Raney nickel or Pd–C effects removal of the chloro substituent in 4-chloropyrazolo[4,3-*c*]pyridines (42–90%)¹⁴⁶ and 4-^{46,234} and 6-chloropyrazolo[3,4-*b*]pyridines.^{34,46}

²³² CIBA Ltd., British Patent 1,115,254 (1968) [*CA*. **69**, 67376 (1968)].

²³³ H. Hoehn and T. Denzel, Ger. Offen. 2,356,684 (1974) [*CA*. **81**, 37544 (1974)].

^{233a} H. Hoehn and T. Denzel, Ger. Offen. 2,333,603 (1974) [*CA*. **80**, 108514 (1974)].

^{233b} H. Hoehn and T. Denzel, Ger. Offen. 2,301,268 (1973) [*CA*. **79**, 115578 (1973)].

^{233c} H. Hoehn and T. Denzel, U.S. Patent 3,979,399 (1976) [*CA*. **86**, 55430 (1977)].

^{233d} H. Hoehn and T. Denzel, U.S. Patent 3,840,546 (1974) [*CA*. **82**, 43413 (1975)].

^{233e} H. Hoehn and T. Denzel, U.S. Patent 3,928,362 (1975) [*CA*. **85**, 46662 (1976)].

²³⁴ H. Hoehn and E. Schulze, Ger. Offen. 2,519,059 (1975) [*CA*. **84**, 44044 (1976)].

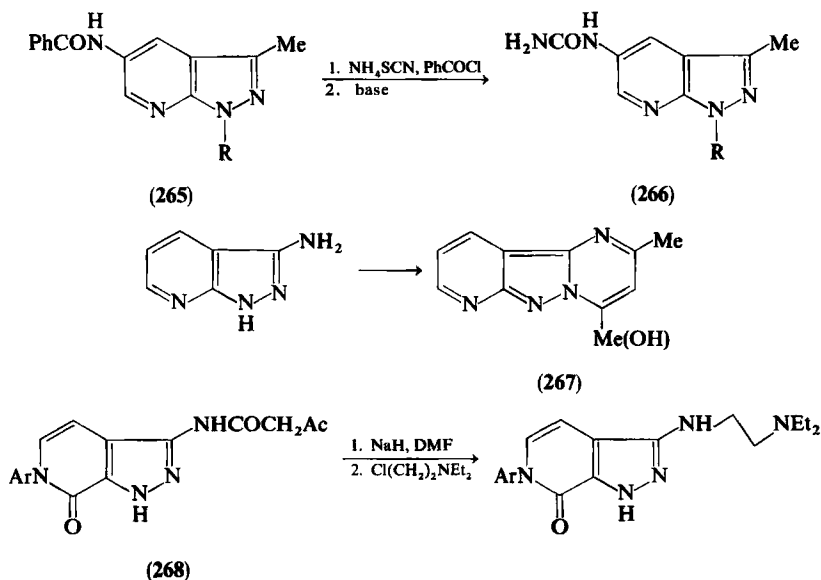
²³⁵ H. Hoehn and T. Denzel, U.S. Patent 3,966,746 (1976) [*CA*. **85**, 177414 (1976)].

3. Amines

In addition to ring syntheses, amines have also been obtained by hydrogenation of a 3-nitro substituent in 5-methylpyrazolo[4,3-*b*]- (92%)¹¹¹ and -[3,4-*c*]pyridines.¹¹⁰ In the pyrazolo[3,4-*b*]pyridine series, decarbonylation of a carboxamido²³² group ($\text{Br}_2\text{-NaOH}$) or hydrolysis of an acid azide⁷⁴ gave 5- and 4-amino derivatives, respectively.

Monoacetylation or -aroylation²³² of the amino function was observed with 3-^{11,15} and 5-aminopyrazolo[3,4-*b*]pyridines²³² and the usual reagents in refluxing pyridine or nitrobenzene. A 1-*H*-7-aminopyrazolo[4,3-*b*]pyridine, however, was rapidly diacetylated in refluxing acetic anhydride.¹⁵⁹ Similar results were obtained with a 2-aminopyrazolo[1,5-*a*]pyridine,¹⁸⁶ whereas a 3-amino analog of the pyrazolo[4,3-*b*]pyridine system afforded a 1-acetyl-3-acetamidopyrazolo[4,3-*b*]pyridine on prolonged reflux.¹¹¹

Condensation of benzaldehyde with 2-amino-3-cyano- or -ethoxycarbonylpyrazolo[1,5-*a*]pyridines gave the corresponding 2-benzylideno derivatives.⁶⁶ A benzoylamino compound (265) was converted to the urea derivative 266.²³²

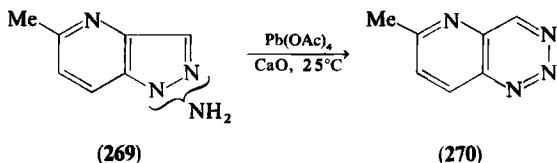


Kocevar *et al.*²³⁶ cyclized 3-aminopyrazolo[3,4-*b*]pyridine to the tricycles 267, using 1,3-dicarbonyl compounds. Similar products were obtained from

²³⁶ M. Kocevar, B. Stanovnik, and M. Tisler, *J. Heterocycl. Chem.* **15**, 1175 (1978); *Heterocycles* **6**, 681 (1977).

the 5-amino analog²³⁶ and 6-aminopyrazolo[4,3-*b*]pyridines.²³⁷ Analogous treatment of the reduced bicycle **127**, however, afforded amides (**268**) that were converted to tertiary amines.¹²⁰

The *N*-amino derivatives **269** underwent oxidative ring expansion to triazine **270**. Analogous pyrazolo[3,4-*c*]pyridines, however, gave only intractable products. The latter system lacked the *peri* interaction necessary for repulsion of nucleophilic attack at the 4-position of the triazine ring.¹⁵⁷



4. Diazonium Salts

Diazotization has been reported for all the pyrazolopyridines, and in some cases the salts have been isolated. A 7-aminopyrazolo[4,3-*c*]pyridine (**191a**) was converted to the corresponding hydroxy compound with sodium nitrite in hot glacial acetic acid.¹⁵⁹ Analogous products were obtained from a 3-aminopyrazolo[3,4-*b*]-¹⁵ and 2-aminopyrazolo[1,5-*a*]pyridine.¹⁸⁶ Decomposition of diazonium salts with hydrobromic acid afforded 3-bromopyrazolo[3,4-*c*]-¹¹⁰ or -[4,3-*b*]pyridines¹¹¹; deamination of 3-aminopyrazolo[3,4-*b*]pyridines was achieved via treatment of the diazonium salts with hypophosphorous acid,¹⁰ titanous chloride,²³⁸ or ferrous ammonium sulfate.²³⁸ Kocevar *et al.*²³⁶ have made a detailed study of the reactions of the latter diazonium salt.

5. Carboxylic Acid Derivatives

In the pyrazolo[1,5-*a*]pyridine series, the reaction of hydrazine with the 2,3-dimethoxycarbonyl derivative afforded the corresponding 2-hydrazide, whereas saponification and decarboxylation gave the 3-carboxylic acid.¹⁶⁹ Further, several 2-substituted 3-carboxamides, -hydrazides, and -carboxylic acids were obtained,^{169,239} using standard methods. Decarboxylation was also reported.¹⁶⁹ A number of transformations of pyrazolo[3,4-*b*]pyridine

²³⁷ R. H. Dong, C. Coquelot, J. M. Bastide, and J. C. Lebecq, *Eur. J. Med. Chem.—Chim. Ther.* **16**, 39 (1981).

²³⁸ B. Stanovnik, M. Tisler, M. Kocevar, B. Koren, M. Bester, and V. Kermavner, *Synthesis*, 194 (1979).

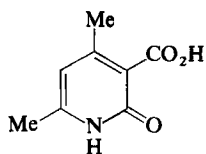
²³⁹ Grelan Pharmaceutical Co., Japanese Kokai, 51,478 (1981) [*CA*, **95**, 115542 (1981)].

5-carboxylic acid derivatives have been reported, including formation of amides,^{232,233,233b,c,d,235,240-242} nitriles,²³⁸ and ketones,⁸⁷ and decarboxylation,^{79,90,95} reduction,²⁴³ and decarbonylation to amines.²³² Several 4-azido⁷⁴ or -hydrazido^{74,244} derivatives were prepared from the corresponding esters⁷⁴ or acids.²⁴⁴

1,3-Diphenyl-5-ethoxycarbonylpyrazolo[3,4-*b*]pyrid-4-one was found to be resistant to saponification.²⁴¹

D. REDUCTION

Formation of reduced pyrazolopyridines has been reviewed in Section IIB, D, F, H, J). Reductive cleavage of the pyrazole ring with Raney nickel as a means of structure identification is confined to 3-hydroxypyrazolo[3,4-*b*]pyridines (9) where reactions were carried out in refluxing ethanol and yields of 2-aminonicotinamides were 15–92%.^{28,30,32-34,38,137,244} The suggestion¹³⁷ that additional hydroxy groups rendered cleavage unsuccessful because of complexation was not observed by other workers. Nitrous acid cleavage of the pyrazole ring to yield pyridones 271 has also been reported.²⁴⁴ Several 1-phenyl-3-methylpyrazolo[3,4-*b*]pyridine-5-carboxaldehydes were reduced to the 5-hydroxymethyl derivatives in excellent yields, using methanolic sodium borohydride.⁹⁵ A 4-substituted analog, obtained by lithium aluminum hydride (LAH) reduction of the ester 61, was further reduced (LAH), via the chloromethyl derivative, to the 4-methyl compound.⁷⁴



(271)

Reduction of 3-acetylpyrazolo[1,5-*a*]pyridine (119b, R¹ = H) with LAH gave the 3-alcohol and not the expected 3-ethyl derivative.¹⁶¹

²⁴⁰ H. Hoehn and E. Schulze, Ger. Offen. 2,159,601 (1972) [*C.A.* 77, 88498 (1972)].

²⁴¹ S. S. Chakravorti, P. K. SenGupta, S. Chaudhuri, and A. Raychaudhuri, *Indian J. Chem., Sect. B* 16B, 161 (1978).

²⁴² T. Denzel and H. Hoehn, U.S. Patent 4,072,681 (1977) [*C.A.* 88, 190885 (1978)].

²⁴³ H. Hoehn and T. Denzel, U.S. Patent 3,983,128 (1976) [*C.A.* 86, 89808 (1977); U.S. Patent 3,928,368 (1975) [*C.A.* 84, 164773 (1976)].

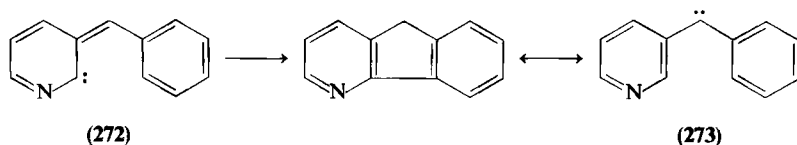
²⁴⁴ P. Papini, M. Ridi, and S. Checchi, *Gazz. Chim. Ital.* 90, 1399 (1960).

E. OXIDATION

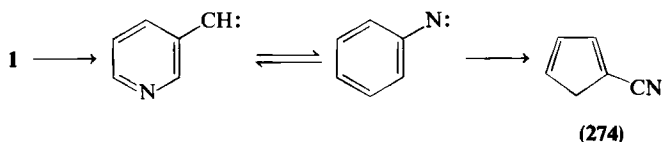
Several 3-substituted pyrazolo[1,5-*a*]pyridines were cleaved to 4-substituted pyrazole-3-carboxylic acids (36–53%) with hot KMnO_4 solution.^{5,168,192} At room temperature, MnO_4^- effected oxidation of 3-(2-furyl)pyrazolo[4,3-*c*]-²⁴⁵ and 5-formylpyrazolo[3,4-*b*]pyridines⁹⁵ to the corresponding carboxylic acids (50 and 63%, respectively). A 6-methylpyrazolo[3,4-*b*]pyridine was oxidized to a mixture of carboxaldehyde (17%) and carboxylic acid (23%), using SeO_2 in refluxing pyridine.²⁴⁶ 1-Benzylpyrazolo[3,4-*b*]pyridine was converted to the 7-oxide (80%), using 3-chloroperoxybenzoic acid,⁸⁸ whereas a 4-thiomethyl derivative underwent air oxidation to the sulfone.^{233b}

F. PYROLYSIS

Pyrolysis of pyrazolo[3,4-*b*]pyridine²⁴⁷ and the 1-phenyl derivative²⁴⁸ proceed by loss of nitrogen gas. The 1-phenyl derivative, at 770°C, underwent 49% conversion to 4-azafluorene. The formation of a carbene (272) from the 3-*H* tautomer was proposed because the alternative carbene (273) is known to lead to mixtures of 1- and 3-azafluorenes.



Pyrolysis of **1**²⁴⁷ at 700–760°C gave the nitrile **274** in 65% yield together with a mixture comprising three reactive components (Scheme 4). Spectroscopic data suggest a mixture of ethynylpyrrole (**275**) and two azafulvenes (**276** and **277**). The formation of the major product is consistent with earlier



SCHEME 4

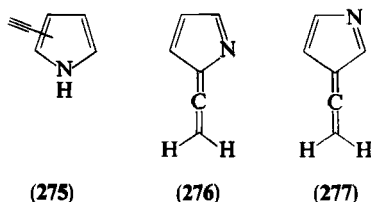
²⁴⁵ R. Motokuni, M. Tanaka, S. Hashimoto, and T. Suzue, Japanese Kokai 78,795 (1977) [*CA.* **87**, 168029 (1977)].

²⁴⁶ H. Hoehn, J. Bernstein, and R. B. Vogt, U.S. Patent 4,062,858 (1977) [*CA.* **88**, 105326 (1978)].

²⁴⁷ W. D. Crow, A. R. Lea, and M. N. Paddon-Row, *Tetrahedron Lett.*, 2235 (1972).

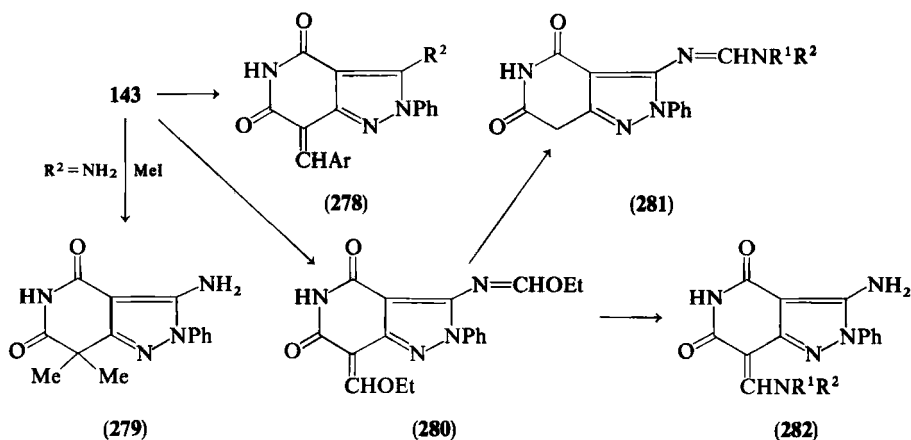
²⁴⁸ C. Wentrup, A. Damerius, and W. Reichem, *J. Org. Chem.* **43**, 2037 (1978).

observations concerning the isomerization of pyridylcarbenes to phenyl-nitrenes, but evidence is given that the by-products may be formed from alternative precursors.



G. MISCELLANEOUS

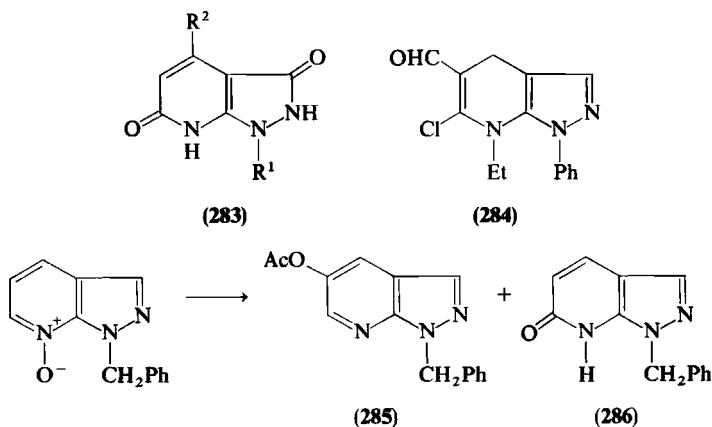
5-Hydroxymethylpyrazolo[3,4-*b*]pyridines have provided a number of derivatives via conversion to the alkyl halide and subsequent reaction with nucleophiles.^{95,249,250} The 7-position in dione **143** ($R^1 = \text{Ph}$; $R^2 = \text{NH}_2$, Ph ; $R^3 = \text{H}$) was sufficiently reactive for condensation with araldehydes, giving benzals (**278**).^{139,140} Further, the amino analog afforded the dialkylated product **279**¹³⁹; however, with triethyl orthoformate, reaction also occurred at the amino function. The compound obtained (**280**) reacted with amines yielding mixtures of products **281** and **282**.¹³⁹ Similarly, diones **283** were converted to 5,5'-dimers.²⁵¹



²⁴⁹ H. Hoehn, U.S. Patent 4,159,380 (1979) [*CA.* **92**, 41939 (1980)]; Fr. Demande 2,430,946 (1978) [*CA.* **93**, 71765 (1980)]; U.S. Patent 4,020,072 (1977) [*CA.* **87**, 117853 (1977)].

²⁵⁰ P. Schmidt, K. Eichenberger, A. P. A. Rossi, and M. Wilhelm, Swiss Patent 416,659 (1967) [*CA.* **66**, 95037 (1967)].

²⁵¹ M. Sugiyama, H. Sawaguchi, and A. Mitsui, Ger. Offen. 2,720,982 (1977) [*CA.* **88**, 106766 (1978)]; Japanese Kokai 135,335 (1977) [*CA.* **88**, 154344 (1978)].



The reduced pyridone **96**, ($R = \text{Et}$) under Vilsmeier–Haack conditions gave the formylated product **284**.¹⁰⁶

Treatment of 1-benzylpyrazolo[3,4-*b*]pyridine 7-oxide with acetic anhydride resulted in β -substitution, yielding the 5-acetoxy derivative **285**.

The expected pyridone **286**, isolated as a by-product in the above reaction, was also obtained by photolysis of the N-oxide in benzene.⁸⁸

IV. Structure and Physical Properties

A. STRUCTURE

1. Bond Lengths and Angles

Bond lengths^{192,214} and certain angles²¹⁴ have been determined for pyrazolo[1,5-*a*]pyridine; the most recent data (CNDO/2 calculation)²¹⁴ are given in Table I.

TABLE I
BOND PARAMETERS FOR PYRAZOLO[1,5-*a*]PYRIDINE

Bond length (Å)		Bond angles (degrees)	
N-1—C-2	1.32	3a-7a-1	105
		7a-1-2	112
C-2—C-3; C-3—C-3a	1.40	1-2-3	107
C-5—C-6; C-3a—C-4		2-3-3a	109
C-4—C-5; C-6—C-7		3-3a-7a	109
C-7—N-7a; C-3a—C-7a	1.34	7a-3a-4	115
N-1—N-7a	1.45	6-7-7a	120
		7-7a-3a	125

TABLE II
DIPOLE MOMENTS OF
PYRAZOLOPYRIDINES

Compound	μ (D)	Reference
1-Phenyl-(1)	2.03	254
2-Phenyl-(1)	4.29	254
(5)	2.15	192, 254
4-Bromo-(5)	2.44	192
7-Methyl-(5)	2.71	192

2. Dipole Moments

Dipole moments calculated by the method of Mazeika *et al.*²⁵² for derivatives of **1** and **5** are summarized in Table II. The results compare with experimental values of 1.5 and 3.4 D for 1- and 2-methylindazole.²⁵³

3. Tautomerism

a. *Aminopyrazolopyridines.* Spectral evidence is given for the existence of **4**.²⁵⁵ and 6-aminopyrazolo[3,4-*b*]pyridines⁷⁸ as the amine form in the crystalline state.

b. *Pyrazolopyridones.* The tautomerism of derivatives containing oxo substituents in the six-membered ring parallels that of the monocyclic pyridones.²⁵⁶ Spectral evidence shows that, in general, pyrazolopyridines of this type exist mainly in the lactam form (cf. pyrrolopyridones⁷). In contrast, Ajello¹⁵⁹ reported an IR absorption at 1652 cm⁻¹ for 7-hydroxypyrazolo[4,3-*b*]pyridine but assigned a lactim structure. Further, a 4-hydroxy-5-ethoxycarbonylpyrazolo[3,4-*b*]pyridine was inferred to exist in the hydroxy form by virtue of hydrogen bonding.^{26,78} This observation contrasts with studies from analogous compounds in the pyrazolo[4,3-*b*]pyridine¹⁵⁸ and pyridine²⁵⁷ series.

²⁵² I. Mazeika, L. Arota, G. Sokolov, and S. Hiller, *Zh. Obsch. Khim.* **34**, 3380 (1964) [*CA*, **62**, 3912 (1965)].

²⁵³ P. Mauret, J. P. Faget, and M. Fabre, *Bull. Chim. Soc. Fr.*, 1675 (1975).

²⁵⁴ S. Hiller, I. Mazeika, and I. I. Grandberg, *Chem. Heterocycl. Compd. (Engl. Transl.)* **3**, 699 (1967).

²⁵⁵ L. V. Sennitskaya, D. Y. Timoshenkova, B. Kiket, Y. A. Pentin, F. F. Blanco, I. A. Korbukh, and M. N. Preobrazhenskaya, *Chem. Heterocycl. Comp.* **13**, 537 (1977).

²⁵⁶ A. R. Katritzky and J. M. Lagowski, *Adv. Heterocycl. Chem.* **1**, 341 (1963).

²⁵⁷ A. Gordon, A. R. Katritzky, and S. K. Roy, *J. Chem. Soc. B*, 556 (1968).

A 4,6-dihydroxypyrazolo[3,4-*b*]pyridine showed IR absorptions attributable to both tautomers,⁹⁰ whereas two carbonyl absorptions (1680–1720 cm^{-1}) were reported for the analogous pyrazolo[4,3-*c*]pyridine.¹⁴⁰

Lykeberg¹⁵⁶ examined the tautomerism of 3-oxo derivative **175** and concluded that it existed in the hydroxy form. The majority of reports on 1- and 2-substituted 3-hydroxypyrazolopyridines,^{19,32,40,44,48,109,116,128} however, quote IR absorptions in the range 1610–1680 cm^{-1} , which are attributed to $\nu_{\text{C=O}}$. Some workers have also reported absorptions due to $\nu_{\text{O-H}}$.^{32,40,44,48} The presence of a significant contribution of the lactam form is more comparable with 3,4-dimethyl-5-hydroxypyrazoles²⁵⁸ than 3-hydroxypyrazoles.²⁵⁹

2-Hydroxypyrazolo[1,5-*a*]pyridine was shown to exist as such, using IR and UV spectrophotometry.¹⁶⁶

B. SPECTROSCOPIC PROPERTIES

Most of the papers cited in Section II report $^1\text{H-NMR}$ spectral assignments and many give IR, UV, and mass spectral data. No attempt is made here to assemble this information, but a few general comments are in order.

1. Mass Spectra

Molecular ions (generally, base peaks in this series of compounds) are often the only peaks reported. The mass spectra of a number of pyrazolo[1,5-*a*]pyridines have, however, been analyzed more fully,^{260–262} with loss of HCN or RCN from the pyrazole ring being the principal fragmentation for each molecular ion.

2. $^1\text{H-NMR}$ Spectra

A correlation between calculated electron densities and observed chemical shifts has been reported for derivatives of **1**,²¹⁷ whereas Black *et al.*²⁶³ have

²⁵⁸ A. R. Katritzky and F. W. Maine, *Tetrahedron*, 299 (1964).

²⁵⁹ A. R. Katritzky and F. W. Maine, *Tetrahedron*, 315 (1964).

²⁶⁰ K. T. Potts and U. P. Singh, *Org. Mass. Spectrom.* **3**, 433 (1970).

²⁶¹ H. Duerr, H. Kober, R. Sergio, and V. Formacek, *Chem. Ber.* **107**, 2037 (1974).

²⁶² A. P. Krasnoshchek, R. A. Khmel'nitskii, A. A. Polyakova, and I. I. Grandberg, *J. Org. Chem. USSR (Engl. Transl.)* **3**, 1546 (1967).

²⁶³ P. J. Black, R. D. Brown, and M. L. Heffermann, *Aust. J. Chem.* **20**, 1305, 1325 (1967).

TABLE III
¹H-NMR CHEMICAL SHIFTS^a OF PYRAZOLOPYRIDINES

Compound	Solvent	2	3	4	5	6	7	Reference
1-Methyl-(1)	CF ₃ CO ₂ H	—	b	8.98	7.97	9.20	—	217
1-Benzyl-(1)	CDCl ₃	—	7.83	7.80	6.86	8.42	—	88
(2)	CF ₃ CO ₂ H	—	9.00	8.69	8.69	—	9.82	111
1-Benzyl-(3)	CDCl ₃	—	8.15	9.10	—	8.37	7.21	146
2-Benzyl-(3)	CDCl ₃	—	8.05	9.15	—	8.26	7.52	146
(4)	DMSO	—	8.33	—	8.55	7.85	8.05	111
(5)	CDCl ₃	7.80	6.38	7.44	6.97	6.62	8.39	213, 215

^a δ (ppm).

^b Value not reported.

discussed the effect of electronic factors on the chemical shifts of these compounds.

¹H-NMR assignments for several simple pyrazolopyridines are given in Table III. Variation of the solvents employed does not facilitate any useful comparison with the ¹H-NMR spectra of pyrrolopyridines.⁷

Chemical shifts for 1- and 2-methyl substituents are observed in the regions δ 3.75–4.28 and 4.01–4.34, respectively.

Dorn and Ozęowski^{62,66,75} have shown that the value of δ CDCl₃–HMPT for H-3 in pyrazolo[3,4-*b*]pyridines is a useful parameter for distinguishing between 1- and 2-substituted derivatives.

3. ¹³C-NMR Spectra

¹³C-NMR data have been reported for pyrazolo[1,5-*a*]-^{169,216,261,264} and -[3,4-*b*]pyridines.^{57,61,62,96} In the former series the effect of substituents on chemical shift has been discussed,^{169,261} and a correlation has been determined between electron density and chemical shift²¹⁶ for **1**. In the latter series, ¹³C NMR has proved useful in distinguishing between isomeric pyridones.^{57,61,62}

4. ¹⁴N-NMR Spectra

Stefaniak²⁶⁵ recorded the ¹⁴N-NMR spectra of **5** as part of an investigation of nitrogen chemical shifts of azole systems.

²⁶⁴ R. J. Pagmire, M. J. Robins, D. M. Grant, and R. K. Robins, *J. Am. Chem. Soc.* **93**, 1887 (1971).

²⁶⁵ L. Stefaniak, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **26**, 291 (1971) [*C.A.* **89**, 128706 (1978)].

5. IR Spectra

Peaks at 1630–1660 and 1590–1616 cm^{-1} in the IR spectra of pyrazolo[1,5-*a*]pyridines have been attributed to $\nu_{\text{C}=\text{N}}$ and $\nu_{\text{C}=\text{C}}$.^{161,167,175,203} Analogous assignments (1585–1625 and 1508–1596 cm^{-1}) have been made for other pyrazolopyridines,^{11,15,24,44,74,90,95,111,157,253} whereas a large number of papers concerning N-unsubstituted derivatives report a complex band, due to $\nu_{\text{N-H}}$, at 2500–3500 cm^{-1} . For pyrazolopyridones, $\nu_{\text{C}=\text{O}}$ is observed at 1625–1720 or 1610–1680 cm^{-1} for a lactam carbonyl in the six- or five-membered rings, respectively.^{19,48,62,104,109,114,116,128,131,140,147,156}

Troitskaya *et al.*²⁶⁶ and Korbukh *et al.*²⁵⁵ have discussed the IR spectra of pyrazolo[3,4-*b*]pyridines in relation to model compounds.

6. UV Spectra

The UV spectra of pyrazolopyridines are comparable to those of pyrrolopyridines,⁷ showing up to three bands at 214–285, 263–298, and 291–374 nm. Galasco *et al.*²⁶⁷ have discussed the spectra of **5** in relation to its electronic structure.

C. BASICITY

The pK_a of **5**¹⁹² and its 7-methyl¹⁹² and octahydro²⁶⁸ derivatives have been reported as 2.47, 2.71, and 2.21, respectively.

ACKNOWLEDGMENT

I would like to thank Dr. J. Parrick and Dr. T. C. Jenkins for helpful discussion during preparation of the manuscript.

²⁶⁶ V. S. Troitskaya, V. G. Vinokurov, J. Grandberg, and S. Tabaks, *Chem. Heterocycl. Compd. (Engl. Transl.)* **3**, 256 (1967).

²⁶⁷ V. Galasso, G. D. Altì, and A. Bigotto, *Theor. Chim. Acta* **9**, 222 (1968).

²⁶⁸ L. N. Yakhontov, M. A. Portnov, E. E. Miklina, M. M. Vaisman, and N. A. Komarova, *Chem. Heterocycl. Compd. (Engl. Transl.)* **8**, 197 (1972).

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